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FOREWORD

“Surely quinine of all things needs no advertising” — such will be the first thought to occur to you on glancing at this book.

On reading the book however you will find that our opinion in this respect fully coincides with yours. Had it been otherwise, we should doubtless have gone about the preparation of this work in an entirely different manner, instead of confining ourselves to collecting scientific articles published in 1923.

As regards articles and reports which dealt with the use of quinine as a malaria specific, we decided that publication of them in full was superfluous, and that we might safely restrict ourselves to short abstracts. We have added a few reports dating back to earlier years.

We trust this work may prove an incentive to you to give special attention to quinine in your range of activity, and to publish your experience. We shall always be pleased to receive your communications on this subject.

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TREATMENT WITH QUININE IN VARIOUS CONDITIONS

BY

J. W. VAN DER SPEK, M. D., Bloemendaal, Holland

OWING to the immense importance of quinine as a specific in malaria, its value in the treatment of numerous other conditions is apt to be overlooked. It may therefore be of interest to refer briefly to some of its other uses.

Binz many years ago demonstrated the fact that quinine is a protoplasmic poison which reduces the excretion of nitrogenous products in the urine; it lessens the rapidity of catabolism in the body, depresses the temperature, and counteracts the elaboration of hippuric acid in the kidneys.

Naturally quinine has been used in many pathological conditions which are accompanied by high temperature, more particularly in pneumonia and typhoid fever. *Weil* regards quinine as a specific in *typhoid fever*, while *Erb*, *Curschmann* and *Caiges* (*Lancet*, 1904) have strongly recommended its use in this condition.

Liebermeister prescribes the drug in doses of $1\frac{1}{2}$ to 3 grams in the morning in order to lower the temperature, and *Erb* obtained excellent results in 180 out of 200 cases of typhoid fever by administering quinine sulphate in doses of $1\frac{1}{2}$ to 2 grams on alternate evenings.

Penzoldt in Magdeburg recommends quinine *hypodermically* in *pneumonia*, and records that in 261 cases the

mortality was 8.8 %, whereas in other hospitals where this treatment was not followed the mortality was 22.5 to 30 %. His routine is to inject 0.5 gram of quinine hydrochloride dissolved in 17 c.c. of distilled water, without the addition of hydrochloric acid, into the abdominal region ; he reports that seldom more than three injections are needed.

Dr. S. Solis Cohen, of Philadelphia, recommends the oral administration of quinine in *pneumonia*.

For oral use, treatment should be commenced with 25 to 35 grains, to be followed by doses of 5 to 15 grains every two, three or four hours. It is advisable to keep the temperature down to 100° F. or even less, and if it should fall to normal, so long as there are no severe symptoms of cinchonism (amblyopia, diaphoresis, tinnitus aurium), there is no cause for alarm ; indeed, the tolerance which patients suffering from pneumonia exhibit to quinine is one of the evidences of its anti-toxic properties.

The best routine method is to make the second dose 15 grains, the third 10 grains, subsequent doses 10 grains every four hours (when the patient is awake) for a day or two, then reducing the quantity to 5 grains every four hours.

Satisfactory results are obtained by giving one *intramuscular* dose of 1.5 grams (20 to 25 grains) of quinine and urea hydrochloride, followed by doses of 5 to 15 grains of the dihydrobromide by mouth every three or four hours.

A 25-50 % solution may be employed for *hypodermic* use.

For *intravenous injection* the initial dose is 1 gram or less of the dihydrobromide or dihydrochloride of quinine and urea, in 10 c.c. of physiologic salt solution. It is rarely necessary to repeat this dose, as the temperature generally falls rapidly to normal, but occasionally it is advisable to

continue the treatment by oral administration of doses of 5 to 10 grains every four hours.

In *influenza* and *pneumonia*, Professor Mouse recommends *hypodermic injections* of quinine as follows: 1 to $1\frac{1}{4}$ grams daily for two days, followed by a daily injection of $\frac{1}{2}$ to $\frac{3}{4}$ gram.

In *whooping-cough* quinine has been favorably reported upon by *Binz*, *Baginsky*, *Baron*, *Teer*, and others. It was found that in many cases the paroxysms of coughing lessened after a few days, the same result being noticed when pneumonia was a complication of whooping-cough.

Pneumonia is said to be prevented by the prompt administration of quinine. The dose is 10 milligrams of quinine hydrochloride per month-age of the child, or 100 milligrams per year-age, three times a day — the maximum dose, however, being 1 to 2 grams daily. *Baginsky* suggests for a child of two years a dessertspoonful every one or two hours of 2 grams of quinine sulphate in 180 c.c. of water. (The disagreeable quinine taste is best disguised with aromatic syrup of yerba santa).

In *hay-fever*, quinine was first recommended by *Helmholtz*, himself a sufferer from this disease. His routine was to inject 4 c.c. of a solution of quinine sulphate (1 gram in 740 c.c. of water) into both nasal cavities three times a day.

To avert a *common cold* at its first onset, $\frac{1}{4}$ to $\frac{1}{2}$ gram (4 to 8 grains) of quinine is often found very serviceable.

ON THE ACTION OF QUININE (UEBER CHININWIRKUNGEN)

BY

Prof. H. KIONKA, M.D., Jena

From the Pharmacological Institute of the University, Jena

WHEN speaking of the therapeutic use of quinine the physician has in mind first and foremost the cure and prevention of malaria by its means. Apart from this however, quinine has a number of other valuable properties which render it serviceable for treatment of other conditions. Yet it frequently happens that the ideas of physicians as to such conditions and indications are confused, probably because the essential nature of the effects of quinine is not generally known or appreciated. It has therefore afforded me pleasure to accept your invitation and I propose to put before you detailed facts on the action of quinine and its chemical allies, leaving out of consideration its effects in malaria which are so well known.

The properties of quinine can be separated broadly into 3 groups. Quinine acts:

1. as a cell poison,
2. as an antipyretic,
3. as a narcotic or a nerve poison.

1. QUININE AS A CELL POISON

Everywhere in the organism and consequently in the individual cell the entire metabolic process is retarded and hindered by quinine. This retardation affects not only

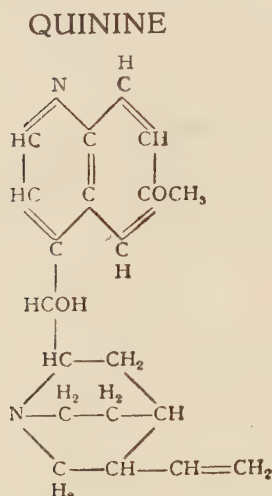
the building up process but also that of breaking up. The smallest dose of quinine therefore produces an economy in the organic process, while large doses as a rule destroy the life of the cell, the entire energy of interchange being extinguished. The probability is that these effects of quinine are due to its action on the enzymes of the cells. It has been repeatedly ascertained that pure enzyme actions are enfeebled or entirely destroyed by quinine and that oxidative and synthetic, as well as hydrolytic and catabolic processes are retarded. The processes of oxidation, above all, are drastically reduced by quinine.

It is this lethal action of quinine on the cell which endows it with its bactericidal powers and with the power to restrict the movements of the leucocytes in weak solutions, and to kill them in concentrated solutions. Quinine produces a torpor of the leucocytes which makes it more difficult for them to pass out of the blood vessels and it is thus able to counteract inflammation and suppuration. On this fact is based the administration of large doses of quinine in *suppurating catarrhs of the respiratory passages* and quinine and quinidine are often found in so-called "Catarrh pills" and "Catarrh powders".

It may be further remarked that in the course of the last few years quinine or similar allied substances have been used for prophylactic purposes in relation to syphilis. Thus there is the well known protective salve "Duanti" introduced by Merck, while the vaginal antiseptic "Agressit", sold in the form of tablets, also contains quinine.

The antiseptic action of quinine, which may easily be proved by its effect in retarding the growth of bacterial cultures, is characteristic in a far higher degree of certain

chemical allies of quinine: the hydrocupreine derivatives. Hydroquinine, which forms from the quinine molecule by dissolution of the double tie, in the vynal lateral chain, may



also be described as methyl-hydrocupreine. Other alkyls may take the place of the methyloxy group in the benzole nucleus of the residue of quinoline and in this way the hydrocupreine derivatives are formed, which, as is well known, were tested by *Morgenroth* as regards their chemico-therapeutic effects on important disease germs. The effect of killing the germs is common to all of them but their degree and efficacy in relation to each pathological bacterium varies. Thus

ethylhydrocupreine, known as *Optochin*, is extremely effective against pneumococci, and isooctylhydrocupreine, called *Vuzin*, particularly effective against streptococci, meningococci and gaseous gangrene bacilli, while the heptyl combination is particularly destructive to staphylococci and isoamylhydrocupreine, known as *Eucupin*, especially effective against vibriones and diphtheria bacilli.

In these hydrocupreine derivatives therefore, we see, along with the general bactericidal action, a pronounced etiotropic effect. This effect, which was first detected in cultures in the test tube, can also develop in the living organism because the blood and tissue juices do not materially impair the disinfecting action.

When using these substances as internal or external dis-

infectants however, it must be borne in mind that the destruction of the micro-organisms is effected, not as with other general disinfectants, by general injury to the cell, or an alteration of the medium, which prevents continuance of the life of the bacteria, but chiefly by the operation of chemotactic properties resulting in a definite and specific coalescence of the particular disinfectant with a perfectly definite kind of bacterium. This, on the one hand, explains the varying qualitative efficacy of these agents in relation to different kinds of bacteria; on the other hand, as we must assume a coalescence of the disinfectant with the bodies of the bacteria, the quantitative efficacy is determined, not only by the substrate to be disinfected (concentration curve), but also by the number of micro-organisms to be destroyed.

The action of quinine on the plasmodium malariae must of course be viewed as a similar etiotropic action.

Mention has been made above of the retarding and, in higher concentrations, destructive effect of quinine on the leucocytes. No doubt however, there are other cells in the organism which are particularly sensitive to quinine and its derivatives and are destroyed by them. There are many facts which suggest that the erythrocytes likewise, under certain conditions at any rate, are specially sensitive to quinine. Blackwater fever, which occasionally occurs during malaria after wrongly timed administration of quinine, hardly admits of any other explanation. Occasionally moreover, after the use of quinine, ecchymosis in the tissues has been observed which can only be explained either by primary injury to the corpuscular elements of the blood and the formation of thrombus, or by injury to the walls of the blood vessels. In every case it is a question of cell injuries. Ecchymosis

of this kind was also found by animal experiments to occur in the internal ear of rabbits after administration of quinine.

Nevertheless those actions of quinine which result in the death and destruction of the cells affected are not always so conspicuous and easily detectable. Quinine is also able, in consequence of the retardation of the processes of oxidation to which reference has been made above, to affect the total activity of the cells in the metabolism of the organism and consequently the organism itself. Thus we know, that the decomposition of albumen in the body is retarded by quinine both in the healthy and the pathologically altered body. In this manner the effect of economy in metabolism is secured which becomes particularly prominent in those instances in which pathological processes of catabolism in a very advanced stage produce a rapid shrinkage of the body substance and consequent decline of strength. This process can, under certain conditions, be inhibited by quinine inasmuch as it retards the catabolic action and along with it all vital processes in the cells.

These effects of quinine in restricting the interchange of energy are of particular importance to the heat economy of the organism.

2. QUININE AS ANTIPYRETIC

Every substance which acts as an antipyretic in the organism must produce its effects in two different directions. In the first place it must exercise a more or less pronounced narcotising effect on the heat regulating centres and in the second place it must, by some other means restrict the heat given off or produced in the organism. Most of the anti-

pyretics in therapeutic use act in the first manner, that is, they increase the giving off of heat by paralysing vasomotion (with consequent dilation of the skin vessels) by increasing the rate of respiration and circulation and by inducing perspiration. Quinine however, acts in the other way on the heat economy; it reduces the production of heat by the retardation as above described of the oxidation and the decomposition of albumen.

These two actions peculiar to antipyretics on the giving off or production of heat cannot however, in themselves, bring about any antipyresis, that is, a reduction of the bodily heat. It is essential that they should also be accompanied by a narcotising action on the heat regulating centres. If the latter were not eliminated they would counteract any increased loss of heat or reduction of heat production produced by the particular agent (as in the case of quinine) and maintain notwithstanding the increased temperature of the body. It must not be forgotten that heat regulation still operates even in fever. This can be seen from the symptoms of defence against mechanical deprivation of heat which the highly feverish body shows in a cooled bath. The temperature having risen to say 104° , the cooled bath only reduces it to 100° which is still an abnormally high bodily temperature. Yet we see that at this temperature the fever patient actually feels chilly and shows distinctly all the symptoms of counter-regulation, seeking to reduce the loss of heat. The heat regulating centre is, so to speak, "adjusted" to a higher temperature in fever. To put it more correctly, the noxa which produces the fever causes the heat regulating centres in the organism to maintain the bodily heat at a higher temperature than the normal. The persistence with which this is done

may be seen from the above described symptoms shown by the fever patient in a cooled bath. If therefore an antipyretic is really to perform the task of bringing down to the normal the bodily heat increase in fever, it must, in addition to its effects on the economy, simultaneously numb the heat regulating centre. This narcotic action sometimes only appears later, or is imperfect and insufficient. It is particularly difficult to obtain in the normal non-feverish organism, because the unpoisoned heat regulating centre is far more resistant and more difficult to narcotise than a centre injured by fever and the poisons of the fever germs. Thus, for instance, after administering quinine, an increase of the oxidation of N-free substances in healthy people is seen, by which regulating action the reduced formation of heat is counteracted by restricting the oxidation of N-containing material. Therefore, in such cases the bodily temperature remains unaltered and may at times even, in consequence of excessive counter-regulation, show a slight increase at the outset. In fever however, the heat regulating centre, which is easily wearied, soon yields to the quinine narcosis and we find a decline in bodily heat, owing to reduction of the heat production without sufficient counter-regulation. The retardation of oxidations is also seen in the respiratory interchange of gases.

Therefore in malaria likewise, we are not justified in attributing the defervescence produced by quinine only to its chemotropic injury to the plasmodia in the blood, but the mechanism of a general antipyresis, as above described, is also a factor.

For this reason, in fevers of other origins, excellent antipyretic effects in quinine are also frequently observed.

3. QUININE AS A NARCOTIC OR NERVE POISON

In the preceding section we have already spoken about a narcotic property of quinine. We have seen that we cannot explain the occurrence of antipyresis after quinine as after any other antipyretic, otherwise than by assuming a narcotic action on the heat regulating centre. In addition to this however, other central and peripheral nerve effects are observable after administration of quinine and its derivatives. The central mental excitement which occurs after large doses of quinine, particularly on long continued use (malaria prophylaxis) and which is designated as "cinchonism" is well known. When quinine has been taken for a long time psychical derangements may occur in the intermediate intervals and not only after the quinine dose: these take the form of defective associative processes, flight of ideas, etc., but they remain mostly of a slight character and as a whole no doubt, contribute to that peculiar psychic complex known as "tropical frenzy".

Effects after quinine are also occasionally observable on the peripheral nervous organs. These are practically all symptoms of paralysis or inhibition; part of these serve a therapeutic purpose, others again are very undesirable accessory effects of the treatment. These effects are therapeutically employed in the quinine treatment of *neuralgia*, many forms of which react more promptly to quinine than to salicylates.

Within this category there is also comprised the extensively applied and in most instances very successful treatment of *whooping cough* with quinine. As is well known, the acid esters of quinine are largely used for this last purpose,

as they are free from the bitter taste of the alkaloid. Recently, hydroquinine hydrochloride has been introduced under the name of "Tussalvin" as a remedy for whooping cough. In all these cases however, we do not know where the point of attack of quinine is situated; quinine is frequently considered to be a direct central analgetic in this case.

Unquestionably peripheral however is the exciting effect of quinine on the uterus, which also appears in the surviving organ detached from the central nervous system. Quinine is therefore frequently administered now as an *ecbolic*.

Peripheral likewise is the causation of the cardiac paralysis occurring after large doses of quinine. It has even been regarded as of muscular effect. It has however been determined with certainty in the case of optochin, that this very undesirable accompanying symptom of the method of treatment is unquestionably bound up with a derangement of the conduction of stimuli.

Finally the fact must be mentioned, as a still more pronounced peripheral nerve effect, that quinine salts possess a distinct *local anaesthetising* effect on nerve endings. On subcutaneous administration this local anaesthesia is usually preceded by pain. Notwithstanding this, hydroquinine derivatives have been directly tried as local anaesthetics.

To what extent the derangements in the eye (amaurosis) and the ear (tinnitus aurium, deafness) which occasionally appear after the administration of quinine, particularly after optochin, are to be regarded as peripheral nervous effects must be left an open question. These symptoms may very well be vascular actions which, in turn, may of course also be vasomotor effects, that is, of nervous origin. The occa-

sional headaches and feelings of giddiness may no doubt also be explained in this way.

Severe quinine poisoning hardly ever occurs with the comparatively small doses used in treatment. From animal experiments we know that very large doses of quinine finally result in central paralysis of the nervous system, which together with the heart paralysis, terminates in extreme stupor and death.

The foregoing is, in general outline, the complex of quinine effects so far as within our present day knowledge. It will have been noticed that this alkaloid and its allied products possess a considerable number of other therapeutically important effects besides the therapeutic efficacy in malaria, which usually forms the chief ground of its appreciation.

Just lately these new pharmacological observations have led to the result that new indications have been formulated for the use of quinine and its derivatives. It almost looks as though we were at the starting point of a new era of quinine treatment.

(*Zeitschrift für aertzliche Fortbildung*, Jena, 1 Sept. 1923, pp. 517—519)

ACUTE LUMBAGO TREATED
BY THE INJECTION OF QUININE AND UREA

BY

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OF common minor ailments there is none which may be more completely paralysing than acute lumbago. In an instant an individual in the full vigour of health may find himself unable to make the slightest movement of the trunk without the most exquisite pain, and he may remain confined to bed for weeks as an absolute cripple. Even in the slightest cases, though the acute symptoms may pass off in a few days, it will be ten days at least before he can stoop with freedom and comfort. In severe cases the slightest movement, or even a sudden noise, may induce a spasm of pain, with a violent contraction of the lumbar muscles, a reflex attempt at protective fixation. The contraction may last for several seconds, and only slowly and cautiously will the patient allow the muscles to relax.

An attack is often brought on by a chill following exertion, such as may occur from sitting in clothes damp from perspiration. An attempted movement produces a spasm of pain, and after that free movement is impossible. The pathological basis is very obscure and probably involves a number of different factors. The circulation in the muscles, diminished by cold, is unable to remove the waste products resulting from recent activity. Probably the muscle responds

to stimuli by an irregular spasm, and a few of its fibres are torn from their origin. This conception would at least explain the fact that it is almost always at a point of attachment that tenderness is most marked.

Though the sudden onset is strongly suggestive of a traumatic origin there is usually a slight but definite constitutional disturbance, and it seems probable that the trauma would be ineffective in the absence of some error in general metabolism, perhaps due to a low grade of infection. But the local symptoms are so severe as entirely to absorb the patient's attention. A close examination will indeed show that the source of these symptoms is even more narrowly localized than the patient imagines, and that the pain spreads from a very small focus characterized by exquisite tenderness to deep pressure. This focus may be situated anywhere in the lumbar muscles, and in addition to its excessive sensitiveness may be marked by a slight local swelling, with an oedema which pits on pressure.

The precise localization of the focus of pain naturally suggests some local form of treatment, and a large number of methods have been recommended. Radiant heat, dry cupping, heavy massage, the insertion of long needles, and the actual cautery, all have their advocates, but the more lenient methods are tedious, whilst the more drastic are somewhat oriental. It occurred to me that the injection of a local anaesthetic would be a rational method to employ, and could at least do no harm. I was scarcely prepared, however, for the instantaneous cures which I have observed, and still less for their permanence.

The anaesthetic I chose was quinine and urea hydrochloride in 1 per cent. solution, and I selected it because

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of the length of time, up to several days, for which the anaesthesia may last. I thought at first that the action might be purely mechanical and I tried normal saline solution, but the effect proved to be only transitory. Five c.c. of the solution is injected through a long fine needle into the centre of the tender spot; within ten minutes the acute pain has entirely disappeared and the patient can move freely; a sense of stiffness remains, and a curious feature is that the patient may complain of a general malaise. It has seemed to me probable that some constitutional disturbance is a regular feature of the condition, but that it is masked by the severity of the local pain.

The following cases illustrate clearly the method employed and the results.

A lady, aged 45, was suddenly seized with severe pain in the right loin. The pain came in spasms so severe that whilst they lasted the right leg appeared to be paralysed and the possibility of a lesion of the lumbar roots was even considered. She lay in bed unable to move, the slightest attempt at movement provoking an attack of pain. Massage, radiant heat, and moist heat only gave partial and temporary relief. Below the iliac crest and just external to the right sacro-iliac joint was an area about the size of a florin, slightly boggy to pressure, and exquisitely tender. Into this area a hypodermic needle was passed till it reached the bone, and 5 c.c. of a 1 per cent. solution of quinine and urea hydrochloride was injected. Ten minutes later the patient found that she could move without producing a spasm, and in two hours she could get up and walk. There were no further spasms, and beyond a feeling of stiffness which lasted for ten days she declared herself cured.

A lady, aged 52, passing through London was seized with violent pain in the lower right lumbar region on attempting to rise from bed in the morning. She had had a previous attack of lumbago which confined her to bed for three weeks (under the care of an osteopath

ACUTE LUMBAGO TREATED BY QUININE & UREA 29

who informed her that she had dislocated her sacro-iliac joint!). There was a tender spot just external to the right sacro-iliac joint, and as the case was one of moderate severity I tried the injection of 5 c.c. of normal saline solution. Marked relief followed, but only lasted a few hours. An injection of quinine was, however, followed by complete relief, and two days later she was able to travel. A month later she wrote to tell me that she had had no further pain and was perfectly well.

It seems to me that a method at once so simple and so safe ought to be generally known and that it must have extensive applications. I have little doubt that it would be equally effective in those simular cases of torticollis and pleurodynia where a localized tender spot is always a marked feature.

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ABORTIVE TREATMENT OF INFLUENZA WITH QUININE

(ABORTIVBEHANDLUNG DER GRIPPE MIT CHININ)

BY

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MY experiences refer to about 25 cases which came under treatment on the first day of illness. In some illness followed a few days after an abdominal operation and was attended by symptoms of dyspnoea, painful breathing, and moderate bronchitis; others were convalescents and others, finally, patients who had previously been operated on and who, when fever first appeared, thinking they had a relapse of their old malady, sent for the surgeon; in two instances, appendicitis was feared because of pains felt in the right abdominal region when breathing.

In all cases, except one where the patient had not taken the quinine, I produced, within 24 hours, absolute freedom from fever, an improvement in the catarrhal symptoms and marked relief of the neuralgic and rheumatic pains; on the other hand a considerable degree of weakness and lassitude persisted for another 2 or 3 days.

On the third or fourth day after the temperature had fallen, nearly all the patients could get up except where the surgical condition necessitated rest in bed. Two ladies in defiance of my wishes, did not remain in bed but got up on the first day they were free of fever, without continuing my

quinine treatment. As a consequence, they were ill for a further 2—3 weeks with slight increase of temperature, marked lassitude, together with nervous troubles especially from the heart. They were confined to their beds and could not resume work for 4—6 weeks.

A hairdresser, who also would not do as he was told, was ill for another two weeks and took nearly three months to make a complete recovery. The only case which was not treated with quinine on the first day, had a high temperature for three days and only then took quinine, but the usually prompt effect failed completely. Treatment with pyramidon-cafeine on *Schoenfeld's* method improved the condition slowly, the patient getting up after $2\frac{1}{2}$ weeks, and making a slow recovery.

I have observed from these cases and others that the treatment of influenza with quinine on the first day of illness is the deciding factor — and further that continued treatment with complete rest in bed and quinine for 2—3 days after the fall in temperature is exceedingly important.

I have persisted with the quinine treatment even in cases of disturbing symptoms such as slight tinnitus aurium and headache as follows:

On the first day of illness when owing to the high fever, an examination and diagnosis were necessary, I gave quinine sulphate 0.3 gram (4.5 grains) still in the evening, followed by abundant hot drinks, such as tea, wine or grog. On the next morning they had 0.3 gram (4.5 grains) quinine sulphate, in the afternoon at 3 o'clock 0.6 gram (9 grains) and in the evening at 10 p. m. again 0.3 gram (4.5 grains). On the third day of illness I gave the patients 0.3 gram (4.5 grains) in the morning, in the afternoon at

2 o'clock 0.6 gram (9 grains) and at midnight 0.3 gram (4.5 grains). On the fourth day they only had 0.6 gram (9 grains) at noon and in the evening at 10 p. m. 0.3 gram (4.5 grains) and from the fifth day onwards, (by which time nearly all the patients were getting up), for about another four days I gave 0.3 gram (4.5 grains) quinine at noon.

Decisive though the results of this abortive treatment were, the results obtained in cases of longer standing or in relapses were in an equal degree disappointing. Especially in the latter the fall of the temperature was so slow and non-typical that the influence of quinine struck me as being highly problematical.

The few cases of influenza which were not treated with quinine at the first onset, were almost equally complete failures and anything but satisfactory in their course. I particularly recall a youth of 14, who came under my care on the 4th day, with slight pleurisy on the right side and suspected appendicitis which induced the general practitioner to consult me. In this case we gave quinine in half the adult quantity, at first in full doses, later, gradually reducing them, for nearly three weeks. The slow fall of the temperature appeared to be entirely uninfluenced by the treatment and progress was very tardy. In the other cases as well, the duration of the illness was 2—6 weeks, the recovery protracted, and for a long time there was much weakness, disinclination and inability to work, with persistent neuralgia, which had partly been complained of at the commencement and partly had developed during the course of the illness. Such neuralgias, besides affections of the nose, ears, trachea and throat have been important characteristics, especially of the last influenza epidemic,

and have been remarkably refractory to all treatment. Here too in chronic cases I tried *Schoenfeld's* treatment of small doses of pyramidon-caffeine together with light-baths; there was however never a rapid effect produced, but a slow and gradual though distinctly successful result.

In the treatment of relapses, as well as in the chronic afebrile forms of influenza, quinine may in my opinion be rejected.

Therefore quinine in the doses indicated above is especially suitable for the abortive treatment of all influenzal infections; in the same way, in very severe illnesses starting with high fever, for instance pneumonia, with very unfavourable conditions appearing almost hopeless on the first day, drastic reduction of temperature can often be obtained in about 24 hours. Neuralgia in such cases occurs either not at all or in a very mild form and muscular and articular rheumatic symptoms disappear after a few days. Mostly I found no tracheitis after the 4th day onwards.

Of course, a trial can be made with quinine in cases which come under treatment later, but it is hardly advisable to continue longer than two days, as — in my experience — a favourable action in the later stages is rare.

(*Therapie der Gegenwart*, Berlin, vol. 64, No. 3, March 1923, pp. 117—118)

PREPARATORY AND AFTER-TREATMENT OF EXOPHTHALMIC GOITRE WITH QUININE HYDROBROMIDE

(DIE VOR- UND NACHBEHANDLUNG BASEDOWKRANKER
MIT CHININ. HYDROBROM.)

BY

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IN the pre-operative period quinine — as well as iodine, arsenic, bromides, iron, belladonna — played an important part in the treatment of exophthalmic goitre. It was recommended chiefly by *Traube* and his followers and also by *Friedreich* and *Baeumler*. It was mostly given simultaneously with iron, while resort to the combination of quinine with digitalis — which was in favour with *Traube*, and which he recommended in incipient compensatory disturbances of the heart (1878) — has been discountenanced in exophthalmic goitre (*Fraentzel*). Later quinine was given successfully especially in America and France in combination with bromine, as quinine hydrobromide: (*Forchheimer*, *Gaultier*, *Chvostek*). With prolonged treatment and large doses, which produced less secondary effects in patients suffering from exophthalmic goitre than in healthy people, quite a number of permanent cures have been observed with the result that quinine was recommended as a diagnostic agent in exophthalmic goitre, resp. myxoedema (*Bram*).

Quinine hydrobromide contains 77 % of quinine and 19 %

of bromide. The reason of the favourable effect of quinine on exophthalmic goitre has only been brought to light by recent experiments.

Wenckebach has, from the researches of *Santesson* and his own clinical observations shown what are the indications for quinine in cardiac conditions. The action of quinine is — apart from the probably unimportant feature of preventing the decomposition of albumen — chiefly on the heart and vessels. At first the blood pressure is reduced — then the frequency of the pulse. It follows therefore that vascular paralysis precedes the paralysis of the cardiac muscle. The development and conduction of the stimulus in the muscle is also impeded. Quinine therefore — according to *Wenckebach* — is not a cardiac tonic, but a depressant and antagonistic to *digitalis*. Consequently its scope of application is found principally in the so-called hyperkineses of the heart. These, *Wenckebach* considers to be: “1. those which depend on the occurrence of excessive and abnormal stimulation of the heart, and 2. cases in which the cardiac muscle responds to normal stimulation by abnormally strong reactions.” To this second group — according to *Wenckebach* — belongs the tachycardia of patients with exophthalmic goitre, with whom — in most cases — the stimulation itself is not increased, but only causes an abnormally strong reaction.

The observations of *Wenckebach* have also been confirmed by others (*v. Bergmann*). Medical treatment of exophthalmic goitre has been very much put into the background by good results of operative treatment.

For the preparatory and after-treatment of cases accompanied by severe tachycardia, and in which we have

ourselves observed grave cardiac complications in connection with even simple ligation of the vessels, quinine can be warmly recommended. We have in the clinic at Leipzig — at the suggestion of *Payr* — tried this remedy for 4 years on over 50 cases, and have compared them with about the same number of cases without such preparatory treatment.

Results were obtained which testify very strongly in favour of quinine as a pre-operative treatment. The patients received about 8 days before the operation and for the same time afterwards 0.25 gram quinine hydrobromide per os 2—3 times daily. The pulse rate went down generally by 10—15 beats per minute during this period of pre-operative treatment. At the same time there began both subjectively and objectively a marked improvement in the existing condition of excitation though in direct sequence to the operation, the pulse rate increased, it only reached, on the average a frequency which was 12—15 beats per minute below that of unprepared patients.

On the day following the operation, the pulse rate declined more rapidly than that of the unprepared patients, and was on the average 15—20 beats per minute lower. The average pulse-rate when the patient was discharged was between 80 and 81 (i.e. normal) in the prepared cases as against 95—96 in the unprepared. At the same time the strength of the pulse remained good throughout, and post-operative conditions of excitation were both rarer and far less serious. In two cases there was no marked cardiac depression after quinine. This must be considered as a proof of an already existing — toxic — degeneration of the heart muscle. Both cases terminated fatally with signs of cardiac insufficiency. In one case only the ligation of the two superior thyroid

arteries was accomplished, in the other also the bilateral cuneate resection.

Observations on the patients during the preparatory treatment may therefore be utilised to the effect of diagnosing severe affection of the cardiac muscle, *if the treatment fails*, and such cases must be excluded from operative action.

(Zentralblatt für Chirurgie, Leipzig, 1923, Nr. 37, pp. 1425—1426)

THE TREATMENT OF PNEUMOCOCCAL
PNEUMONIA BY INTRAMUSCULAR INJECTIONS
OF QUININE URETHANE

(DIE BEHANDLUNG DER PNEUMOKOKKENPNEUMONIE MIT
INTRAMUSKULÄREN CHININ-URETHAN-INJEKTIONEN)

BY

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Frankfort Medical Society, official report of meeting 5th February 1923

PROVIDED treatment is begun as promptly as possible, intramuscular injections of 0.5 gram quinine hydrochloride with 0.5 gram urethane in 5.0 grams water, given on the 1st, 2nd or 4th day of treatment will effect a considerable shortening of the course of croupous pneumonia. Out of a series of 427 cases taken from 2 different areas over a period of 6 years, 173 have been treated thus, while 254 were used as *simultaneous* control cases of the same age, so far as possible of a like nature, and, except for the injections, treated in the same way.

Thus by carefully eliminating epidemiological and individual differences, a reliable estimate of the therapeutic value of the treatment can be arrived at. With quinine urethane the mortality amounts to 6.3%, in early cases (commencing treatment within three days of initial shivering) 5.3%, in control cases 19.8%. A rough estimate of the duration of the fever in cases treated on the 1st and 2nd day of illness respectively was 2.9 and 4.6 days, with control cases 8.5 days. In early cases there was a total of 56% definitely afebrile before the end of the 4th day, control cases only 3.5%.

The marked improvement in the general condition, especially of the circulatory system which is chiefly displayed in the improvement of the dyspnoea, is due to the lessened toxicity.

Quinine urethane is only effective in dealing with pneumococcal but not other infections. Administered per os, it has no action on pneumonia, even if given repeatedly in large doses.

After an intramuscular injection, a quinine "pocket" forms at the site of injection from which there is released into the blood a far higher concentration of quinine than if administered orally. The quinine is stored up in the infiltrated lung of the patient, so that f.i. four days after the injection, when the presence of quinine is not demonstrable in the blood, and only with difficulty in the urine, it can still be identified in the lung in considerable concentration.

(Münchener Medizinische Wochenschrift 1923, Nr. 17, p. 548)

PARENTERAL THERAPEUTICS OF QUININE IN INFANTILE BRONCHO-PNEUMONIA

(ZUR PARENTERALEN CHININTHERAPIE DER
LUNGENENTZÜNDUNGEN IM KINDESALTER)

BY

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CONSEQUENT upon the striking results obtained by *Aufrecht* and *Cahn-Bronner* in broncho-pneumonia by the administration of hypodermic injections of quinine — results which far surpassed those achieved by using the same remedy per os — *Friedberg* was encouraged to investigate this form of treatment in the very common condition of infantile broncho-pneumonia. (*Archiv für Kinderheilkunde*, vol. 71, 1922, p. 264).

In the endeavour to avoid the necrosis which occasionally follows *subcutaneous injections* of quinine he tried first of all to administer the drug intravenously.

This however, did not prove satisfactory, as in the first place the therapeutic effects did not come up to expectations, and further, this method appeared to be attended with a certain amount of danger from thrombosis of the vein, oedema near the vein, etc.

He then tried, with greater success, — taking of course all the usual precautions — *intramuscular injections* of 10% solutions of quinine urethane (quinine hydrochloride 1 gram, urethane 0.5 gram, aq. destill. 10 grams) as used by *Aufrecht*.

This solution was properly warmed, and the syringe rinsed with warm alcohol, ether, or physiological salt-solution before taking up the requisite dose. This method, it was always found, prevented quinine necrosis which is most probably due to the crystallising out of quinine needles when the temperature of the solution is lowered.

Of the above Friedberg injected intramuscularly the following scale of doses —

For babies	1 —1.5 c.c.
" children 2— 5 years old	1 —2.5 c.c.
" " 5—14 " "	2.5—4 c.c.

once daily, for the first two days, missing the third day, and repeating the injection if required once on the fourth day. As a general rule no further injections were necessary, although in a few cases treatment had to be continued up to say 10 injections in a fortnight.

In many cases Friedberg found that in 6—12 hours after the first injection a marked improvement took place, temperature dropped, dyspnoea and cyanosis, as well as the quivering of the nares in breathing, disappeared with remarkable rapidity. The child sat up in bed and quickly recovered his appetite. Indeed the success of these injections was exceedingly striking.

Perhaps the most interesting feature was that in spite of the marked improvement in the general condition the physical signs in the lungs could still be detected a number of days afterwards.

Friedberg found that not all cases but in particular incipient broncho-pneumonia reacted so remarkably to the treatment. Of 58 incipient cases treated by him, 52 responded favourably in a strikingly quick way, indeed in most cases,

after the first dose, so that a second or third injection was not necessary. In this way he succeeded very frequently in aborting the attack.

In 53 out of 68 cases of *longer standing broncho-pneumonia* very encouraging results were observed, although reaction was not so rapid as in the incipient cases.

Finally *Friedberg* found that the cases so favourably influenced by this treatment were cases of pneumococcal broncho-pneumonia. On the contrary, in the epidemic of 1921—22 he found no benefit whatever from the treatment in post-influenzal broncho-pneumonia.

(Archiv für Kinderheilkunde, Stuttgart, Vol. 71, No. 4, pp. 264-269.
Report by Prof. Dr. J. de Bruin in Nederlandsch Tijdschrift voor
Geneeskunde, Haarlem, January 6, 1923, p. 59)

ON THE TREATMENT OF CROUPOUS PNEUMONIA BY INTRAVENOUS AND INTRA- GLUTEAL INJECTIONS OF QUININE

(UEBER DIE BEHANDLUNG DER KRUPPÖSEN LUNGENENTZÜNDUNG
MIT INTRAVENÖSEN UND INTRAGLUTÄALEN CHINININJEKTIONEN)

BY

M. JOHN, M. D.

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AUFRECHT wrote as long ago as 1905, in the *Berliner Klinische Wochenschrift*, of the remarkable results attained in cases of pneumonia by treatment with hypodermic injections of quinine urethane solution.

In the same way, without knowing of the publication of those investigations, we have — since 1917 — treated a large number of cases of pneumonia by intravenous and intragluteal injections of quinine. The reason we adopted quinine was because we hesitated to administer to hospital patients who for the most part were not admitted until the third to the seventh day of the attack, intravenous injections of optochin, a remedy which does not act well, given per os, and which has in some cases caused serious injury to the optic nerve.

In the meantime *Cahn-Bronner* published (*Zeitschrift für klinische Medizin*, 1919) an article in which — on the basis of a study of 156 cases in the clinic of Strassburg — he expressed himself as being in entire agreement with *Aufrecht* regarding the extraordinarily successful results of subcutaneous quinine injections in the treatment of pneumococcal pneumonia.

If therefore — notwithstanding the foregoing — I too record the observations which we have made, along the same lines, during the past five years in the Hospital, and in the years 1917—1918 at the Reserve Military Hospital, where we had very nearly two hundred cases of acute pneumonia, I do so in order that I may stimulate further research on a method of treatment, the value of which every one can verify for himself because of its simplicity.

The salt we use is the quinine bi-hydrochloride (readily soluble in water) of which 2 c.c. of a 25 % solution — that is about $\frac{1}{2}$ gram quinine for adults — is injected intravenously or intragluteally, while for enfeebled patients and to children proportionately less is administered.

In the early days of our adoption of this treatment we gave according to the severity of the condition — 3 to 8 or more injections per day or every other day. Since however *Cahn-Bronner* published the result of his investigations, i.e. that quinine injected subcutaneously can be detected in the system and retains its potency for days, asserting therefore that the maximum therapeutic efficiency of quinine is reached already after three injections, we decided eventually to give the quinine, at first, once or twice intravenously and following this twice, or in long-standing conditions three times intragluteally.

Where the veins are in bad condition, it is recommended to give the injections intramuscularly; there has never been any noticeable irritation as is often the case with subcutaneous injections; on one occasion a severe and stubborn necrosis was observed due to some of the solution getting into tissue surrounding the vein.

So far as the other unpleasant accessory effects are con-

cerned, it may be recorded that *Aufrecht*, to his intense surprise, hardly ever (certainly more rarely than when administering the drug internally) had a complaint of tinnitus aurium after giving injections.

Baermann in Sumatra was struck just as well — after an investigation of over 600 cases of pneumonia — by the absence of toxic symptoms or amblyopia when the quinine or even the optochin is injected and not administered per os. We have made considerably more than 2000 quinine injections (not all, by the way, for pneumonia) and we have never experienced trouble with the optic nerve, although once, deafness lasting several hours was observed. On the other hand, immediately after an intravenous injection of quinine, a pneumonic patient collapsed for about five minutes with complete unconsciousness, diminished reflexes, accelerated pulse, stertorous breathing and clonic spasms especially of the arms. The intragluteal injection given on the next day was borne without any trouble. With one female patient displaying thyroid trouble with cardiac excitability a quinine injection produced a tachycardia of short duration.

We take this opportunity of recalling the fact that according to experiments, carried out by *F.B. Hofmann* on isolated hearts of mammals the quinine produces a reduction of the systole and the frequency and, as is assumed by *Frey*, *Boden* and *Neukirch* as a result of their experimental and electrocardiographical researches, undoubtedly weakens the power of the heart. *Winterberg* states that after an intravenous injection of 1 gram quinine, severe attacks of tachycardia followed, and *Frey* observed in two patients, probably these with an idiosyncrasy in relation to quinine,

after small doses, dangerous conditions of unconsciousness with absence of respiration and pulse.

Even if in experiments on animals (which, by the way, can hardly do justice to the incalculable conditions in the human organism), quinine may cause harmful cardiac conditions, and if clinically — on occasion — untoward effects due to hypersensitiveness to the treatment make their appearance, nevertheless quinine treatment cannot be rejected outright. Cases of death (such as have happened after salvarsan injections which in spite of that are still administered) have not yet occurred, and unpleasant symptoms also arise with other intravenous injections, e.g. Caseosan.

According to clinical experience the harmful effect of quinine on the heart is not of great importance, indeed the impression received is on the contrary — as we shall see shortly — that the activity of the heart is greatly improved by injections of quinine.

A few typical cases will now be recorded, showing the effect of quinine given parenterally on the development of pneumococcal pneumonia.

1. Emil Kr., aged 30 years. Admitted to hospital 8. III, 1917 (sixth day of illness) completely unconscious, temperature 39,4, pulse 140, in a condition of stupor, soils bed. Pupils dilated and reactionless. Pneumonia in the right inferior, middle and left parietal lobe. 0,5 gram quinine given intravenously.

9. III. After the second injection clearer on the whole, mentions his name, can take nourishment, still very restless, pulse 108.

10. III. Almost quite clear, knows his family, explains how the illness started etc. Resolution in the left parietal lobe, right lung completely involved: commencing engorgement in the left inferior lobe.

11. III. Return of dulness of sensorium.

Subsequently cessation of the resolution in the right lung and on the 14. III the illness terminated fatally.

The *autopsy* revealed that all three lobes of the right lung and the left inferior lobe were involved.

2. Otto P., age 40 years. Fell ill suddenly two days before, with ague and pain in the right side of chest.

29. III, 1917 (third day of illness) taken to hospital. Badly nourished, wasted appearance, dirty yellowish complexion, marked cyanosis and dyspnoea, faint pulse, 120—130. Infiltration of the right inferior lobe.

Intravenous injections of 0.5 gram quinine were administered daily and on the sixth day of sickness the right inferior lobe was involved, on the day following the left inferior lobe and part of the right superior lobe. On the eighth day of illness, resolution in the right inferior lobe, which extended to the other affected portions of the lung, on the eleventh day of illness temperature fell by lysis. The case proceeded without complications, pulse up to fall of temperature never under 120.

3. Dr. K., schoolmaster, age 32 years. After suffering from a cold for several days, developed on the 10. III, 1919 ague, cough and sputum.

13. III, 1919 (fourth day of illness) admitted to hospital. Enfeebled physical condition, no cyanosis, no dyspnoea. Pulse 100—110, regular and fairly powerful. Infiltration of right inferior lobe. Leuc: 16 400. Injection of 30 c.c. "Reconvalescent serum".

14. III. Pneumonic involvement also in the right parietal lobe, slight cyanosis, pulse 120—130 and weaker. Injection of "Reconvalescent serum" repeated and suprarenin injected subcutaneously hourly.

15. III. Right lung completely involved and in addition, symptoms in the left parietal lobe, bronchial breathing, marked cyanosis and dyspnoea, and commencing tracheal rales. Faint pulse, 130—140 per minute. In the presence of these signs, injection of 0.5 gram quinine, which after two hours very much improved the action of the pulse, now 100. Cessation of tracheal rales, less cyanosis and dyspnoea.

16. III. Further injection of quinine, temperature fell by lysis, commencing resolution in the right inferior lobe.

17. 3. 19 Afebrile. Uneventful convalescence.

4. Dr. L., age 25 years. Fell ill the day previously with ague, pains in the right side of chest.

15. XI, 1920 (second day of illness) admitted to hospital. Fairly well nourished and moderate general condition. Slight cyanosis, pulse 130, regular, faint. Dulness in the right inferior lobe, bronchial breathing. Leuc. 21 100.

16. XI. 0.5 gram quinine. After a few hours pulse became 100 and did not increase on subsequent days. No return of cyanosis.

19. XI. Right parietal lobe also attacked. The following day resolution in the right inferior lobe. Temperature fell by lysis.

21. XI. Resolution in the right parietal lobe and from thence onwards temperature became normal.

5. Mrs. M., age 48 years. 17. IX, 1920 fell ill with ague simultaneously with her husband who died a few days later at home.

23. XI. (seventh day of illness) admitted to hospital. Prostrated. Looked seriously ill. Dyspnoea. Cyanosis. Distinctly jaundiced appearance. Urobilinogen + + +. Temperature $39-40^{\circ}\text{C.}$, pulse 140, small and faint, slightly irregular. Lower lobes on both sides attacked.

On the 23rd, 24th and 25th XI, 0.5 gram quinine was administered intravenously. Pulse distinctly improved after the first injection, dropping to 100—110, regular, and after the 25th XI, between 80 and 90. Corresponding fall of temperature.

27. XI. Resolution commenced.

6. Hans R., sergeant, age 23 years. Previous history, in August 1915 and March 1919 inflammation of the lungs.

21. XII, 1921 migraine, ague, pain in right side of chest.

22. XII, 1921 (second day of illness) admitted to hospital. Enfeebled and generally in emaciated condition. Slight cyanosis. Temperature 39.4 , pulse 120, regular and of fair volume. Pneumonia in right lower lobe. Leuc. 5 200 (sgm. 53 %, polynucl. 27 %, juvf. 3 %, mononucl. 2 %, lymph. 15 %).

24. XII. Left lower lobe also attacked. In the right, resolution commencing. Pulse 100—110. Temperature $39^{\circ}-40^{\circ}\text{C.}$ Leuc. 13 600 (sgm. 42 %, polynucl. 33 %, myel. 3 %, juvf. 8 %, mononucl. 1 %, lymph. 13 %).

27. XII. Left lung completely involved. Dyspnoea and cyano-

sis more marked, pulse 108—112, Leuc. 23 200 (sgm. 36%, polynucl. 35%, juvf. 7%, myol. 3%, mononucl. 7%, lymph. 12%).

Up till now the patient had received each time 0.5 gram quinine on the 23rd and 24th intravenously and on the 26th and 27th intragluteally.

29. XII. Condition of lungs unchanged. Temperature 39—40° C., pulse 100—110. Very restless, at times slightly delirious. Leuc. 20 500 (sgm. 44%, polynucl. 31%, juvf. 6%, myol. 4%, mononucl. 1%, lymph. 14%).

31. XII. Condition of lungs unchanged. Temperature 39.7° C. Pulse 120—124, worse, more marked cyanosis. Leuc. 25 600 (sgm. 61%, polynucl. 28%, juvf. 5%, myol. 1%, mononucl. 1%, lymph. 4%). Condition of the blood decidedly better. After another intragluteal injection of quinine, the pulse improved and cyanosis decreased.

2. I. (13th day of illness). Temperature fell by lysis, resolution in left lung. From the 4th January free from fever. Leuc. 11 700 (sgm. 51%, polynucl. 14%, juvf. 5%, myol. 2%, eosinoph. 1%, mononucl. 1%, lymph. 26%).

From the above outlines of cases, which, on the whole, reflect our general experience, the following points stand out in the consideration of the parenteral treatment of croupous pneumonia with quinine:

The actual *duration of the disease* in all cases is hardly shortened to any marked degree where treatment cannot be commenced until after the 3rd till 5th day of illness. Nor is the spread of the disease to other lobes prevented. If it is possible, however, to commence injections on the 1st or 2nd day of illness, it is in our experience by no means a rare occurrence to observe even after the first injection a decrease in temperature, indicative of the arrest of the disease.

Fever is, except in cases of early treatment, not influenced.

The *general condition* of the patient improves in a remarkable manner. Dyspnoea and cyanosis decrease and there is

an amelioration in the sensorium. Absolutely unconscious cases return to consciousness (case 1). Under the influence of quinine, patients show no signs of serious indisposition. Children at first apathetic and inert, begin to sit up and play. In short, the disease is — in many cases — deprived of its after all serious and dangerous character.

The *condition of the pulse* improves (as may be distinctly noted in cases 3—5) in a remarkable way often within a few hours after the first injection. The pulse becomes slower and fuller in volume, even regular, if it has been irregular before (case 5). Even after all heart stimulants have been unsuccessfully used, the pulse-frequency may decrease from 130—140 to 100 (case 3) and remains at this rate throughout the whole course of the illness, a remarkable contrast to a continued high temperature of 39°—40° C. In cases of protracted duration the change in the condition of the pulse is not so remarkable, though here too we were able to record a pulse of 100—110 in a severe illness lasting 2 weeks and longer.

If injections of quinine do not influence the pulse, then, in our experience, it is practically impossible that any stimulant should correct the weakness of the circulation. Should however, a pulmonary oedema appear, arising from inflammatory or circulatory conditions, calcium intravenously is indicated. Following *Bernhard's* report a short time ago on research into the applicability of intravenous calcium therapy, we have, in over 20 cases of pulmonary oedema, seen the tracheal rattle almost with the certainty of an experiment disappear after an injection of calcium, mainly only temporarily, but in three cases at least permanently, which means the saving of the patients' lives.

As regards the behaviour of the *leucocytes*, the number of which are of considerable importance in pneumonia — indeed the diminution of which is regarded as a distinctly unfavourable symptom — during the course of the quinine treatment, there is observable a marked increase from low to high values, though whether this is “post hoc” or “propter hoc” it is impossible to say in an isolated case.

Further the more or less distinct *alteration in the blood-count*, which occurs with every case of pulmonary inflammation due to the increase of the polynuclear leucocytes, juvenile forms and myelocytes, appears to demonstrate a real improvement in each case. As we have only studied this question, however, for about a year on 50 cases of pneumonia, it is still too soon to form a decided opinion on these very baffling details.

Now, what *mortality* do we find in cases of pulmonary inflammation treated with quinine?

During the following years we have used quinine by injection thus:

1917	in 51 cases of pulmonary inflammation,	9 died (18 $\frac{0}{0}$)
1918	„ 50 „ „ „ „ „	, 17 „ (34 $\frac{0}{0}$)
1919	„ 18 „ „ „ „ „	, 2 „ (8,11 $\frac{0}{0}$)
1920	„ 25 „ „ „ „ „	, 5 „ (20 $\frac{0}{0}$)
1921	„ 22 „ „ „ „ „	, 2 „ (9 $\frac{0}{0}$)
1922	„ 31 „ „ „ „ „	, 3 „ (9,6 $\frac{0}{0}$)

Commenting upon the above, it is necessary to remark that it deals — almost without exception — with desperate cases, mostly admitted to hospital on the 3rd till 5th day of illness or later, and that it was a mere accident that in the hunger year 1918, the mortality among patients suffering from inflammation of the lungs was particularly heavy.

This last fact is very strikingly demonstrated by the vital statistics kindly placed at my disposal by the Allgemeine Knappschaftsverein, Bochum. From these it appears that there were the following deaths in the manufacturing districts during the years :

1917	of	2119 miners who fell ill	. .	580 = 27,38 %
1918	under	3603 cases of illness	. . .	1519 = 42,01 %
1919	"	2377 " " "	. . .	540 = 22,29 %
1920	"	2361 " " "	. . .	589 = 24,09 %

As has been pointed out, the diagnosis of such cases as inflammation of the lungs is certainly made too often and this error can only be approximately corrected through the mortality table. Fatal results should in reality show a higher percentage. In the years 1911—1916 of 40—60 cases of croupous pneumonia which were treated yearly in our department, we had — roughly — an annual mortality of 29—41 %. In comparison with and in contrast to the statistics of the Allgemeine Knappschaftsverein, Bochum, which also included less serious cases, whereas we only admitted to hospital the severe cases, the mortality figures for the years 1919—1922 were therefore remarkably low, although not so favourable as reported by *Cahn-Bronner* in his cases : "Of these treated with quinine 6,4 % died, and of the control cases 25 %, or after subtracting the moribund cases 20 %".

How are we to picture to ourselves the rationale of the action of quinine, which, according to the investigations of *Cahn-Bronner* only displays its full effect when administered "parenterally"?

Cahn-Bronner found that only very minute quantities of quinine are absorbed into the blood from the alimentary canal, and even then are excreted very rapidly ; whereas

after only one injection of quinine, it can be clearly detected in the blood after several hours.

Furthermore, his researches have enabled us to arrive at the notable conclusion that, after repeating an injection, and thus forming what may be termed a reserve of quinine under the skin, there is observable a certain accumulation in the blood which benefits the general condition and particularly the affected lungs, thus probably getting at the root of the disease. The question is only, whether it can and to what extent it does influence the cause of the infection.

According to the researches of *Morgenroth* and his followers quinine possesses, in contrast to optochin, at least in the test tube and animal experiment, no bactericidal qualities whatever, in respect to the pneumococci. It is not to be considered that a chemical remedy can destroy infections in the diseased system, say on a "therapia magna sterilisans" basis. And yet, if we attempt to explain the influence of quinine on pulse and general condition otherwise than by its directly antagonistic influence on the septic process, (a point I shall discuss below) the indisputable fact of the markedly increased leucocytosis from a unfavourably low to a high count during the quinine treatment, as well as the general improvement of the blood test, are hardly intelligible except on the assumption that either the defensive forces of the system have been fortified or that the septic processes have been weakened. The wellknown fact that quinine is only active in pneumococcal pneumonia but not — for example — in influenzal pneumonia, surely points to a weakening of the pneumococcal infection by quinine. If this connection actually exists, then the remarkable improvement in pulse and general condition may be readily understood.

But since — according to *Wenckebach* — quinine has “a depressing, dulling and relaxing effect on the cardiac muscle” and in many cases of arrhythmia perpetua can restore the heart to its normal rhythm (*v. Bergmann, Frey, F. B. Hofmann* a.o.) it would appear that the apparent steadying of the pulse in pneumonia after an injection of quinine may conceivably be caused by a direct action on the heart.

It is hardly necessary to say that the treatment of pulmonary inflammation with injections of quinine is very easily carried out in ordinary practice. Colleagues of mine who have adopted this method of treatment, entirely confirm our results, and they are themselves continually agreeably surprised at the much more favourable course of the disease and the increasing rarity of a fatal result.

(*Deutsche Medizinische Wochenschrift*, Leipzig, No. 12, March 23, 1923, pp. 381—382)

THE TREATMENT OF PNEUMONIA

BY

John T. MACLACHLAN, M.D., Rothesay, Scotland

THE treatment of pneumonia by *Dr. Wynn* of Birmingham with pneumococcal vaccines, as related by *Dr. Newell* in the issue of the British Medical Journal for April 21st, 1923, p. 676, gives such splendid results that it will be obviously the duty of general practitioners to test the validity of the conclusions, since the ordinary treatment of this disease by drugs etc. is very disappointing. It is not an over-estimate to state that, in the case of adults, there is one death in every four or five patients attacked by this disease. As the last four cases of pneumonia that I had occasion to treat all recovered, I am tempted to state the treatment adopted.

The youngest was a woman aged 38 with double pneumonia; the oldest was a man of 70; the other two were about 60. Alcohol was used freely in all cases, and the patients were allowed to take whisky and soda-water whenever they desired it. It was left to the patients to take it or leave it according to their own inclination. Digitalis was given in sufficient quantity to reduce the pulse rate from 120-100; 1 grain of quinine was administered every two hours with the suitable dose of digitalis, preferably in pill form. If the temperature was 104° F. 1 or 2 grains of antifebrin were added to the pill, for a high temperature, in my opinion, has an exhausting effect on the heart. Opium gr. $\frac{1}{4}$ was

given to soothe the cough and the patient. The prescription was therefore as follows:

R. Quinine gr. 1
P. digitalis gr. $\frac{1}{2}$ or $\frac{1}{4}$
Antifebrin gr. 1 or 2
P. opii gr. $\frac{1}{4}$

Ft. pil. I or pulv. I. Sig: one to be taken every two, three, or four hours, according to circumstances.

The quantity of digitalis and antifebrin is determined by the pulse rate or the rise of temperature. On these lines we protect the heart, and the results are excellent.

(British Medical Journal, London, May 26, 1923, p. 897. Memoranda)

SELECTED NOTES

THE number of deaths from malaria throughout the whole world reaches an enormous total every year; James (1920) estimates that in an ordinary year there are 1,300,000 deaths from endemic malaria in India alone.

(William Fletcher, M.D. *Notes on the treatment of malaria with the alkaloids of Cinchona*, p. 58)

Reports received from the Red Cross in Russia indicate that there are now some 3,000,000 cases of malaria in the republic West of the Ural mountains. In Georgia one-half of the population are affected and at the village of Sam-bourtaile near Tiflis two-thirds of the total population have died of malaria.

(British Medical Journal, Febr. 3, 1923, p. 219)

By March 1923 between 60 per cent. and 70 per cent. of the whole population were suffering from the disease, the incidence being between 90 per cent. and 100 per cent. in most of the districts.

(*Notes on the epidemiology of malaria in South-East Russia* by Melville D. Mackenzie, M.D., senior medical officer, Friends' Russian famine relief unit, South-East Russia. *Lancet*, Dec. 8, 1923)

While typhus diminishes, malaria increases, even undergoing a quasi-pandemic spread (our Institute of tropical

diseases and its director, Dr. Marzinovski, estimate the number of cases in a year to be 10.000.000).

(L. Tarassévitch. *Expansion pandémique de la malaria en Russie*. Causerie faite à une séance de la Société de pathologie exotique, publiée dans les Bulletins de cette Société, Tome XVI, 1923, No. 2, pp. 71—74)

The principal diseases from which death resulted were malaria (11.44 per 1.000), dysentery and diarrhoea (1.78), pulmonary tuberculosis (1.76), and beri-beri (0.33). Malaria was thus, as always, the most prevalent disease.

(*Malaria in Malaya*. British Medical Journal, Dec. 1, 1923, p. 1058)

On the other side, the Albanian Government has asked the Health Committee of the League of Nations to help it in the preparation of a systematical campaign against malaria, a disease which ravages Albania and injures its economical development.

(*La lutte contre le cancer et le paludisme*. Presse Médicale, June 23, 1923, Nr. 50, p. 1057)

Malaria is with endemic syphilis the prevailing disease of the population of Anatolia. (v. Dühring. *Aerztliche Kultur-aufgaben in der Türkei*. Arch. f. Schiffs- & Tropen-Hyg., vol. 20, Nr. 4). Although extant in Asia Minor from the remotest times, it has only in our days undergone such an extension that it must be considered not only as a heavy burden on the agricultural population, but even as a plague threatening the very existence and development of the population of Anatolia. In the particularly severely affected regions of Anatolia, it is very often found that the incidence

and the death rate of malaria exceeds many times the incidence and the death rate of all other contagious diseases put together.

(Dr. Eugen Bentmann. *Kriegsärztliche Erfahrungen in Anatolien*. Supplement to the *Archiv für Schiffs- & Tropen-Hygiene*, 1923. Vol. 27, Nr. 1. p. 64)

Quinine is the only remedy known for malaria, but will cure all cases, if taken properly. If not taken regularly for a sufficient length of time or if the doses taken are not large enough it usually fails to destroy all the malaria parasites and often after a period of a few days or a few weeks the person gets sick of malaria again.

(The "Standard treatment for malaria", recommended by the National Malaria Committee and approved by the United States Public Health Service)

There is only one specific treatment: quinine.

(Le Dantec, XVIIth French Medical Congress, Bordeaux, 27-29 Sept. 1923.)

It must be laid down as a principle, that quinine is the specific medicament for malaria, because it destroys the plasmodium by direct toxic action, as can be ascertained *in vitro* and *in vivo*.

(Dr. Paiseau. *Le paludisme*. Traité de pathologie médicale et de thérapeutique appliquée, publ. sous la direction de Emile Sergent, L. Ribadeau—Dumas et L. Rabonneix. Tome XIV, 1921, p. 437)

In conclusion, malaria is, above all, like trachoma, and like typhus, a disease of destitute peoples. If we may be allowed to echo in a modified form the motto of a great

coloniser, Marshal *Bugeaud*, we would say, that, instead of: *Ense et aratro*, the motto of the modern settler ought to be, since *Maillot* and *Laveran*: *Aratro et quina*.

(Edm. et Et. Sergent. *Les facteurs sociaux de la décroissance du paludisme*. Bull. Soc. de pathologie exotique, 1921, Vol. XIV, pp. 658-662)

The specific remedy for malaria is quinine, as mercury is for syphilis. Of the many substitutes for quinine which have been proposed, not one can be compared with it and as *Manson* so justly says in his work: *Tropical Diseases*, 5th ed. p.118: "In serious cases to use any drug to the exclusion of quinine is culpable trifling."

(E. Jeanselme et E. Rist. *Précis de pathologie exotique*, 1909, p. 67)

In conclusion the writer would impress upon the profession the vital importance of continuing quinin therapy for several weeks in all malarial patients, as only in this way can we hope to cure the infection and prevent our patients from becoming "carriers" of malaria. The objection commonly urged against the long continued use of quinin, that the drug causes digestive disturbances, anemia, and distressing headache and vertigo, is not true, if it be administered in the dosage recommended, and it has been the writer's experience that the vast majority of individuals, after the first few days, can take from 10 to 15 grains of quinin per day for months without unpleasant symptoms or injury to health. Fortunately, one soon becomes accustomed to those doses of the drug and unless special attention is called to the fact, forgets that quinin is being administered. Even if some slight discomfort is occasioned by the drug, it is as

nothing, when compared with the discomfort of repeated attacks of malaria and the consequent profound effect of them upon the general health.

(Lieut. Col. Charles F. Craig, Medical corps U.S. Army, in his article *Malaria* in vol. V of *The Oxford medicine*, by various authors, edited by Henry A. Christian, M.D. & Sir James Mackenzie, M.D., 1921, chapter XXXII, *Infectious diseases and diseases due to animal parasites*, p. 739-796)

The quinine salts are the paramount remedy for malaria.

(Report of the Commission for the fight against malaria created in 1920 by the Central Council of Hygiene of Holland)

Quinine has given proofs of its value as a specific against malaria.

(Supplement to the above report)

Modern medicine possesses in quinine a paramount remedy for the cure of malaria.

(Minerva, Rome. November 1, 1923. p. 746)

As proved by centuries of experience, cinchona bark, from which quinine is made, possesses the power of destroying the parasites and curing the infection. But it will not generally destroy all the parasites in the body unless it is given in sufficient doses and continued for several months; and as long as a single parasite remains alive in the blood, infection is continued and the patient may be subject to relapses.

At least 5 grains ($\frac{1}{2}$ gram) of sulphate of quinine should be taken by an adult patient every day without fail for four

months; but he should consult a medical man regarding details of treatment.

(Prof. Ronald Ross. *Prevention of malaria*)

Acton (1920) has found that a relapse occurs after treatment in about 10 per cent. of subtertian cases, and 75 per cent. of benign tertian; but there is the same chance of cure with each subsequent course of treatment, the parasites do not become quinine resistant.

(William Fletcher. *Notes etc.*, p. 51)

Articles pointing out the futility of quinine treatment have appeared recently in the English newspapers, where they probably attract but little notice and do but little harm.

Now, all medical men with long experience of tropical practice will recognize the truth of the following extract from an editorial which appeared in a recent number of the Indian Medical Gazette (1921): "What can be claimed for quinine is, that if properly used it will rapidly relieve the symptoms due to malaria parasites and, if properly followed up, it will prevent the parasites from causing death or serious damage to the patient *it is criminal to do anything to deter the patient from using this life and health saving remedy.*"

(William Fletcher. *Notes etc.*, pp. 57 and 58)

Were it possible to carry out investigations in animals with the *plasmodia* of human malaria, the hypothesis of quinine-fastness could be readily put to the test.

But in this instance, as well as in all the others which we met with, the resistance to quinine vanished so soon as we

gave the drug to the patient ourselves and saw that he swallowed it.

Undigested quinine tablets were never found in the excreta, but occasionally they were picked up under the beds.

(William Fletcher. *Notes etc.*, p. 67, 77 and 80)

During a fairly long life in the tropics, I gave to the whites, only tablets of quinine hydrochloride, excepting the cases, which for that matter were very few, in which I was forced to make injections because of gastric intolerance or comatose state. The patients are thoroughly and rapidly cured, so much so, that here in the Congo I never resort to the large doses recommended by certain authorities. I very seldom exceed the dose of one gram per day. As regards prophylactic treatment, I often have patients who complain of symptoms of cinchonism, and I often find quinine in the urin. With such experience, it will be readily understood that I should be very loth to be deprived of so valuable a treatment.

(H. Seidelin. Meeting of October 11, 1922 of the Société de pathologie exotique. Bulletins of the Society, 1922. Vol. XV, p. 686)

“In order to secure generalization of the preventive use of quinine, quinine of good quality, cheap and in a handy form must be available to the public. The only handy form at the present time, is, so far as we know, the tablet of quinine hydrochloride; if it is of good quality, and is taken properly it gives every satisfaction” (*Laveran*).

(Léger and Bédier. Meeting of October 21, 1922 of the Société de pathologie exotique. Bulletins, vol. XV, p. 870)

To revert to the use of solutions, so hard to absorb, or bulky capsules, fragile and very hygroscopic, would be to

take a step backwards which does not appear justified and which can only injure the work of anti-malaria prophylaxis.

(Maurice Langeron, Société de pathologie exotique, meeting of December 13, 1922. Bulletins, vol. XV, p. 961)

If quinine is truly the specific for malaria which the voice of experience proclaims it to be, then any success of the campaign against it will result in multiplying the number of deaths from the disease.

(William Fletcher, *Notes etc.*, p. 58)

All attempts made to substitute for quinine an equivalent artificial product in the treatment of malaria, have failed.

(Prof. Albert Richaud. Chair of pharmacology and *materia medica*, Paris Medical University, opening lesson, March 1923)

A NEW CASE OF AUTOCHTHONOUS MALARIA

(UN NOUVEAU CAS DE PALUDISME AUTOCHTONE)

BY

PAUL CRAMPON, M.D., Lille, France

Report by the Medical Society of North France in February 1923

WE are indebted to M. P. Crampon for reporting this case contracted in the Valley of the Lys, where other cases had been previously pointed out by M. Pierre. In this instance a young man had been admitted to the Clinic with the diagnosis and symptoms of influenza; the occurrence of a typical crisis however suggested the possible diagnosis of malaria.

Microscopic examination of the blood disclosed the presence of numerous tertian malarial parasites.

The virus appears to have been introduced by foreign workpeople, particularly Russians, who are very numerous in these regions, being engaged in reconstruction work.

The presence of *Anopheles* has been frequently detected in the Valley of the Lys.

(*Presse Médicale*, Paris, 1923, No. 22, March 17, p. 263)

CINCHONA FEBRIFUGE, QUINETUM AND QUININE

BY

J. J. HOFMAN, Pharm. D., The Hague, Holland

REFERRING to the articles in the "Pharmaceutisch Weekblad", Amsterdam, (1923, No. 6 and 7) on *Cinchona febrifuge*, Dr. A. Groothoff in "De Indische Mercur" of June 29th 1923 gives an explanation of the value of this remedy and a review of its history and of the retarding influence it has had on the development of the cultivation of quinine in Java.

On reviewing the prices of quinine from 1824, when the price of a kilo amounted to f1350 (£ 112) up to the present day, it is found that the high prices before 1880 limited its use on any large scale, for fighting malaria.

Many attempts were made to replace quinine by other preparations: the *Société de Pharmacie de Paris* offered a prize of 4000 francs, to which the Secretary of War added the sum of 8000 francs, for the synthetical preparation of quinine, and in 1855, *Sonnenschein* even informed *Hasskarl*, that he had almost succeeded in synthetising quinine in his laboratory, so that it was entirely unnecessary to bring over the quinine tree to Java.

Yet it was only by using more up to date and better methods of cultivating the quinine tree in the Dutch Indies that it became possible to supply the world with quinine, at a reasonable price.

The results of this cultivation, which was started in 1851, under the direction of *Junghuhn* with *de Vrij* as chemical adviser, were rather discouraging in the first years, chiefly on account of a rather inferior variety, *Cinchona Pahudiana*, having been chosen. After the death in 1864 of *Junghuhn* who was succeeded by *van Gorkom*, it was decided that this variety should no longer be cultivated, and an entirely different course was adopted. However, *de Vrij*, who pursued his chinological studies in the Netherlands, where he acted as adviser to the Department, continued to protest against this decision. *De Vrij* also had a special preference for the variety *Cinchona succirubra*, which he had got to know for the first time in British India. Though recognising that quinine has the strongest action of all alcaloids, *de Vrij* thought that the exclusive use of quinine would render the other alcaloids valueless and would send up the price of quinine.

He therefore gave a prescription for the preparation of this mixture of alcaloids, which he called *quinetum*, and which enabled every chemist to prepare those alcaloids himself.

Van Gorkom and *Bernelot Moens* however realised that the final aim of the cultivation must be the production of quinine and that this aim was promoted by cultivating a bark with a great percentage of quinine and only few other alcaloids, which is especially the case with *Cinchona Ledgeriana Moens*. For decocta and other pharmaceutical preparations, the cultivation of *Cinchona succirubra* was indicated.

In British India, which had made a speciality of the cultivation of *Cinchona succirubra*, part of it was used for preparing *quinetum*, the remainder was sent to Europe, but

could not be sold at a profit as the percentage of quinine was too low.

Although it was to be anticipated in 1876, that the cultivation of the Ledger variety would yield a sufficient supply for the world consumption, *de Vrij* succeeded in inducing the Government to make experiments in the Dutch Indies with the preparation and application of quinetum, which gave very satisfactory results in British India.

One of his pupils, *Eydman*, an army chemist, was instructed to prepare it, and the Chief of the Medical Service distributed the *Cinchona febrifuge* to the different hospitals, where its action was tested. The results were not satisfactory; its use against pernicious forms of fever was deemed inadvisable, and it was not considered very suitable as a substitute for quinine, because of its unstable composition and its accompanying effects which were sometimes dangerous.

The composition indeed varied greatly and the analyses gave percentages of:

Quinine	2.9—22.2	per cent.
Cinchonidine	24.0—60.4	" "
Cinchonine	18.0—54.0	" "
Quinidine.	2.8— 5.4	" "
Amorph. alkaloids	0.4—21.0	" "

During *Groothoff's* stay in the Dutch Indies, the quantity of quinetum then still existing, was used for preparing quina-wine; 4 grams were dissolved in diluted hydrochloric acid and added to 1 litre of Teneriffe wine.

The controversy about quinetum has since lost its interest, as the supply of quinine is nowadays more than sufficient and its therapeutical value in all respects is open to no doubt.

In British India where quinetum is only used by the natives, its results seem to be satisfactory. It may be that economic reasons play some part here, more especially the impossibility of using the British Indian bark to advantage in the manufacture of quinine.

But it certainly would not make for progress, if the attempt were made in Holland or its colonies to direct attention to a product which is far inferior in point of reliability to quinine.

(Pharmaceutisch Weekblad, Amsterdam, October 6, 1923, pp. 1095—1096)

FREQUENCY AND TREATMENT OF THE MALARIAL SPLENOMEGALIES IN CHILDREN

(FRECUENCIA Y TRATAMIENTO DE LAS ESPLÉNOMEGALIAS
PALÚDICAS DE LOS NIÑOS)

BY

ZENOBIO CÁRDENAS SINCLAIR, M.D., Lima, Perú

IN Lima (Perú) 68% of the cases of malaria affecting growing children were accompanied by marked splenic enlargement, while 70% were infected with *Plasmodium vivax*.

Swelling of the spleen was found to be as common in town as in country patients.

Intensive treatment with quinine was usually promptly effective.

The author first gives to children of 8—13 years 0.5 gram quinine sulphate, and to children of 4—8 years 0.3 gram three times *a day* for a week. Then 0.3 gram and 0.2 gram respectively three times a day for a week. The treatment is suspended for a week, and then the same dose is repeated for a week. Finally, in the sixth week, after another week's cessation 0.3 gram and 0.2 gram respectively are administered once daily only.

The quinine is always given *per os*, but when commencing the treatment, sodium sulphate is given first.

(La Crónica médica, Lima, Perú, 1922, N. 705. Report of Prof. Dr. P. Mühlens, Hamburg, in Archiv für Schiffs- & Tropen-Hygiene, vol. 27, 1923, p. 46.)

THE ANTI-MALARIA CAMPAIGN AND THE
QUININE SUPPLY

THOUGH, as shown by this book, quinine and its various preparations are very much used in many varieties of disease, quinine itself remains nevertheless, first and foremost, the only and indispensable remedy for malaria.

As there still are large tracts of the earth's surface where this disease rages to the point of being mistaken for plague, because of its contagious and deadly character, the supply of an efficacious and sufficient quantity of quinine has become rather a social problem than a question of purely medical interest.

There is no necessity to dwell upon the fact that a population suffering from malaria loses its strength, its energy and its working power to such an extent that its standard of accomplishment is much below that of a healthy nation.

Whereas colonization was done in the olden times on the lines of the motto: "*Ense et aratro*", it is based at the present time on the principle: "*Aratro et quina*", for this reason, that a colony cannot prosper if planters and natives suffer from malaria.

The great importance of the anti-malaria campaign is also proved by the interest shown in this problem by the Health Committee of the League of Nations. It is natural that in the debates of this Committee, attention has been drawn to the question of quinine supply for the population of

malarial countries and as it was discovered that this supply was far from satisfactory, the inference was drawn that the production of quinine was not sufficient for the needs of the world.

An opinion to this effect was given by a medical authority at the Congress of Saint-Paul-de-Loanda, which was held from the 16th to the 23rd of July 1923. Its conclusion was no doubt based on the experiences gained during a survey made for the purposes of this Congress and which extended to a large part of Tropical Africa. Both this conclusion and that arrived at by the Health Committee of the League of Nations have been carefully considered by us.

In connection with this opinion, which is no doubt that of many other personalities interested in the anti-malaria campaign, we think it interesting, from a general point of view, to give a few details which may dispel the false ideas existing on the subject.

There is no truth in the assumption that the production of quinine is insufficient for the world's needs. On the contrary, there is a large surplus production of cinchona bark and this is sufficiently proved by the following data:

We are able to use the exact figures of the crops of the 110 Dutch East Indian cinchona plantations, which supply about 90% of the total production. Below we give the figures since 1921, and we add the forecasts of 1924 crops. This last figure is based on data given by the plantations themselves and may be considered as accurate:

In 1921	513.608 kilograms of quinine sulfate in bark						
„ 1922	534 545	”	”	”	”	”	”
„ 1923	534 624	”	”	”	”	”	”
„ 1924	621 800	”	”	”	”	”	”

Of these barks the following quantities in quinine form only have been used during the years 1921, 1922, 1923:

In 1921	358 705 kilograms of quinine sulfate
„ 1922	394 949 „ „ „ „
„ 1923	470 000 „ „ „ „

The net result of this is that production considerably exceeds consumption.

Moreover, it must be borne in mind that on March 1st 1924 the stores of Amsterdam contained:

24 971 bales of cinchona bark containing about	122 400 Kg. of quinine sulfate
On the same day 4 418 bales of cinchona bark were on their way from Java to Amsterdam, containing about. . .	19 880 „ „ „ „
While 21 643 bales of cinchona bark were stored in the plantations in Java containing about	97 400 „ „ „ „
Total about	239 680 Kg. of quinine sulfate

Considering these data, it is not surprising that the growers have thought of resorting to restricting the crops, so as to economize on salaries, storage, insurance and other expenses, caused by such large quantities in stock.

In connection with this matter we give below an extract from the annual report for 1922 of the Government Cinchona plantation at Tjinjirean (Java):

“In 1922, the total crop amounted to 982 412 kilos of bark. In 1921, it had reached 1 201 335 kilos of bark. During the year under report therefore 218 923 kilos less than in 1921 had been harvested, a restriction which was due to the reduced needs of manufacturers, consequent upon the decreased demand for quinine salts on the world’s market”.

We are convinced that the managers of several cinchona plantations have adopted the above measures in order to limit the unsold stocks and to cut down the costs of production.

As will be seen in complete contrast with the opinions expressed in Geneva and Saint-Paul-de-Loanda, there is a considerable overproduction of quinine.

Indeed, there has never yet been an insufficient production. Production has always exceeded consumption and the rational method used at the present time for the cultivation of cinchona affords a guarantee that there will be no change in this respect.

The series of illustrations, for which we are indebted to the kindness of *Dr. Kerbosch*, director of the Government Cinchona plantation at Tjinjiroean (Java), gives sufficient proof of the care with which this cultivation is carried on and the scientific methods used.

We see then, on the one hand, a series of countries with an inefficient anti-malaria organisation due to the local lack of quinine and on the other hand, a quinine production which is larger than the world's consumption.

Our Office will be very pleased to act as intermediary, and form the connecting link, and we beg those medical authorities interested in the anti-malaria campaign, to address themselves to us.

It would be desirable, that wherever there is malaria, the State should attend to the distribution of quinine. Here Italy has shown the way, and the great success obtained in that country, as clearly shown by the following tables, has already prompted several governments to follow its example.

We also show here a few reproductions of different packings used by certain governments for selling the quinine to the population at cost price. Such sale is made through Post Offices, State tobacco shops and other establishments open to the public.

MORTALITÀ PER MALARIA E CACHESSIA PALUSTRE IN ITALIA

negli anni dal 1887 al 1923

Anni	Cifre assolute	Cifre proporzionali ad 1,000,000 di abitanti	Numeri indici
1887.....	21033.....	710.....	
1888.....	15987.....	536.....	100
1889.....	16194.....	539.....	
1890.....	15647.....	517.....	87
1891.....	18229.....	599.....	101
1892.....	15531.....	506.....	85
1893.....	15301.....	496.....	83
1894.....	15296.....	492.....	83
1895.....	16464.....	526.....	88
1896.....	14023.....	445.....	75
1897.....	11947.....	377.....	63
1898.....	11378.....	356.....	60
1899.....	10811.....	336.....	56
1900.....	15865.....	490.....	82
1901.....	13558.....	417.....	70
1902.....	9908.....	303.....	51
1903.....	8517.....	259.....	44
1904.....	8463.....	256.....	43
1905.....	7845.....	236.....	40
1906.....	4871.....	146.....	25
1907.....	4231.....	126.....	21
1908.....	3478.....	103.....	17
1909.....	3533.....	104.....	17
1910.....	3621.....	105.....	18
1911.....	4420.....	127.....	21
1912.....	3161.....	90.....	15
1913.....	2664.....	75.....	13
1914.....	2045.....	57.....	10
1915.....	3835.....	105.....	18
1916.....	5060.....	137.....	23
1917.....	8407.....	237.....	40
1918.....	11487.....	325.....	55
1919.....	5163.....	138.....	23
1920.....	3443.....	91.....	15
1921.....	3456.....	91.....	15
1922.....	3188.....	86.....	14
1923.....	2274.....	61.....	10

a) *Recrudescenza del periodo di guerra.* Per la valutazione della mortalità per malaria del 1918, bisogna tener conto della grave pandemia influenzale, la quale iniziò durante il 2° semestre e determinò una elevata mortalità negli individui con progressiva infezione malarica. Tale mortalità non può, perciò, assurgere ad espressione veridica del fenomeno epidemologico, e deve ritenersi molto superiore a quella che si sarebbe verificata ove non fosse intervenuto tale eccezionale fattore.

b) *I dati relativi agli anni 1919-23 sono presuntivi*

MORTALITÀ PER MALARIA E CACHESSIA PALUSTRE IN ITALIA

negli anni dal 1887 al 1923

Cifre proporzionali ad 1.000.000 di abitanti



CINCHONA CULTURE IN JAVA,

24 HELIOTYPES

The native forest in the Preanger Regenschappen (Java).



Cinchona-tree in the forest of Java, planted by Junghuhn, who from 1856-64 was the manager of the "Gouvernements-Kina-Onderneming" (Governments-Cinchona-Plantation) in Java. He held the mistaken view that it was necessary to plant the young Cinchona-trees in shadow, in order to obtain a strong development, as well as a high degree of alkaloid.



Cutting down the forest. The best results are obtained by laying-out the regular Cinchona-plantations on ground, from which the natural forest has been cleared.



How the bare field is terraced in order to avoid the washing-away of the fertile top-soil
by tropical rainfall.



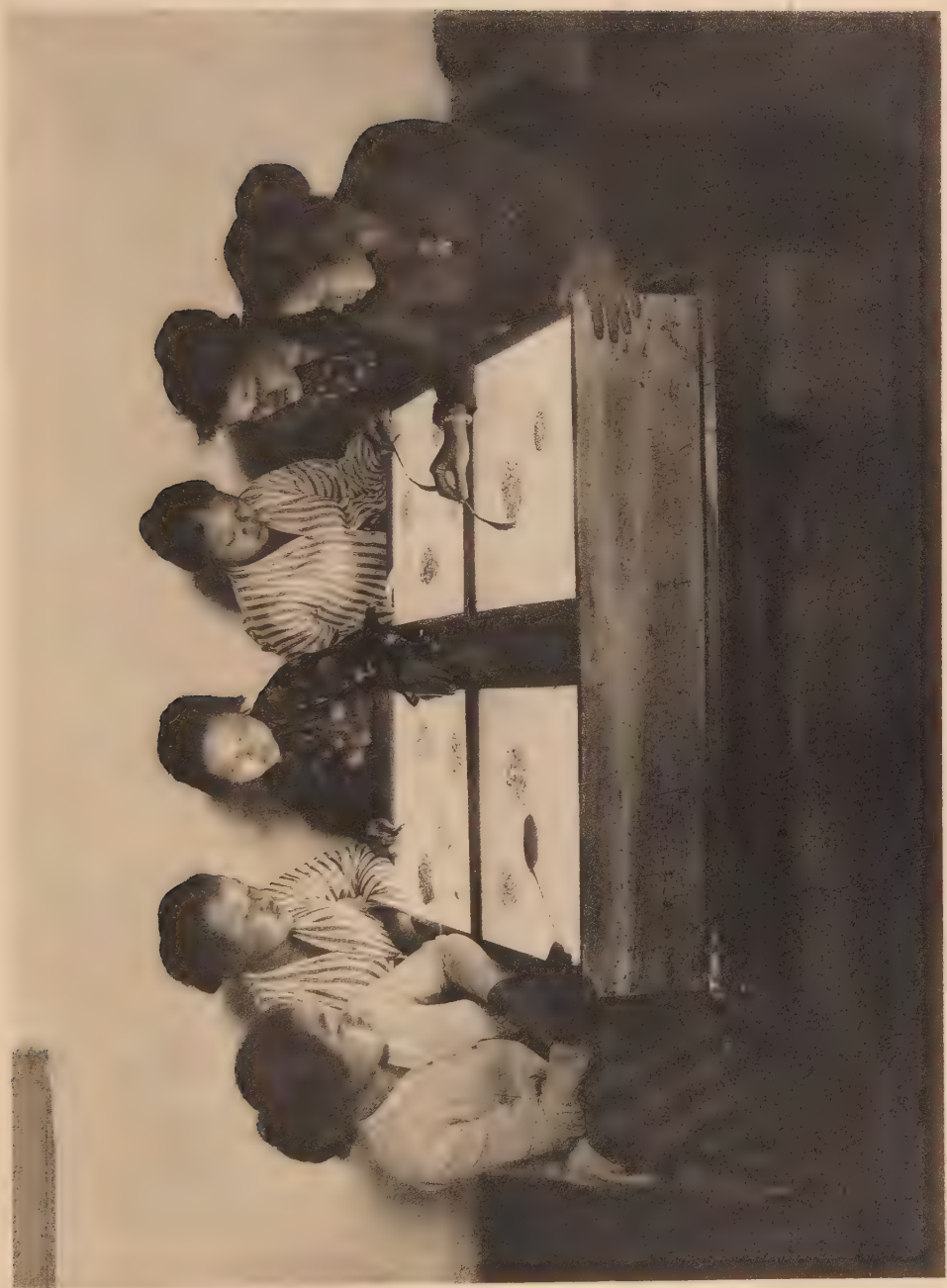
Cinchona Ledgeriana in blossom.



The collection of the seed on a Cinchona-plantation.



The selection of the seed. This is done by examining its transparency when placed on ground glass plates.



The sowing of the Cinchona-seed on the seed-beds.



From the seed-bed the young Cinchona-plants are taken to the nurseries.



Grafting of *Cinchona Ledgeriana* on to a *Cinchona Succirubra* stock.



Nurseries with grafts of *Cinchona Ledgeriana*, 5 months after grafting.



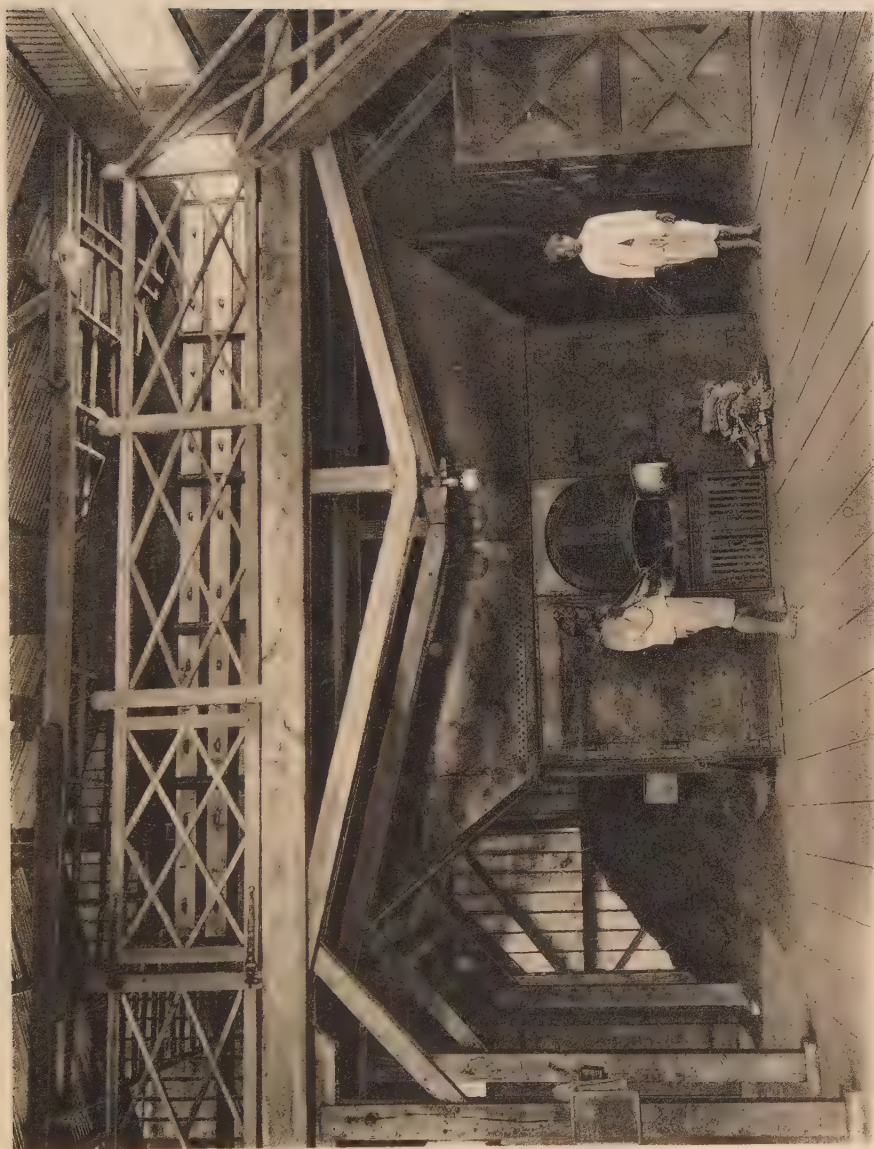
Plantation with 12 year old grafts of *Cinchona Ledgeriana*.



The gathering of Cinchona-bark.



Drying-process of Cinchona-bark in a dry-installation. On some plantations the combination of both systems is practised.



The cleaning of dried Cinchona-bark from small pieces of wood and other impurities.



The packing of Cinchona-bark.



Bales being loaded into native carts (roda's) for transport to the station.



Cinchona Ledgeriana-trees, 57 years old, which were
obtained from seed, imported from South-America.



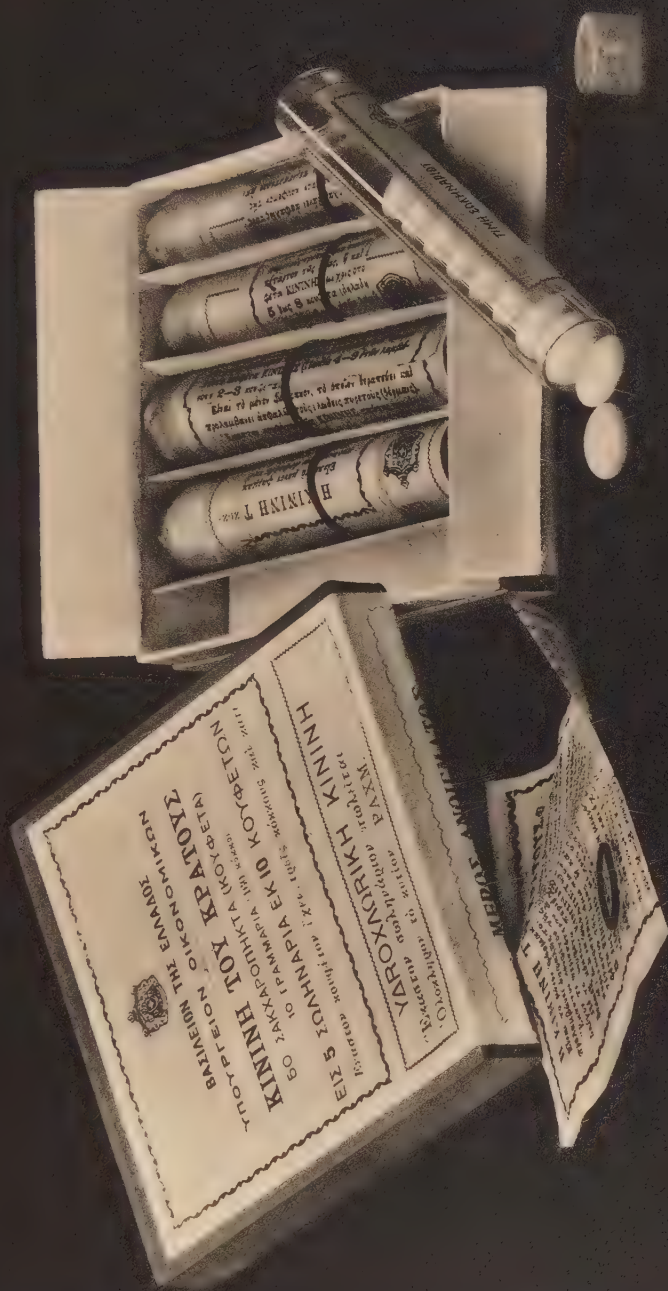
The famous Cinchona Ledgeriana-graft No. 38n, containing at the age of 7 years a percentage of 18,50 % quinine sulphate in the bark of the trunk.



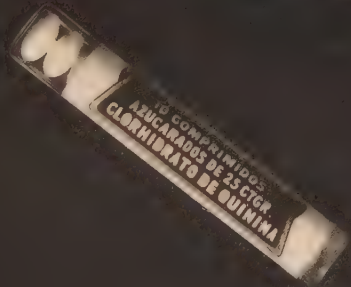
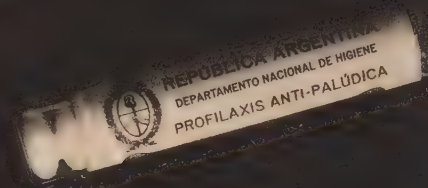
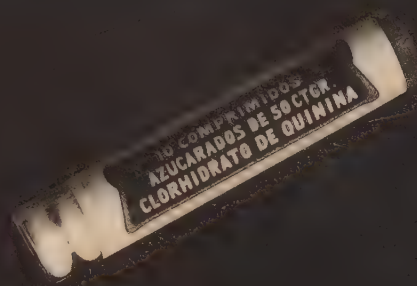
Laboratory of the "Gouvernements-Kina-Onderneming" (Government-
Cinchona-Plantation) in Java. Chemical Department.



One of the most practical methods of administering quinine in the fight with malaria is the sugar-coated quinine-tablet. Several Governments are selling small packages of it to the population at cost price. Next page shows the usual package in Greece.



A few Argentine packages.

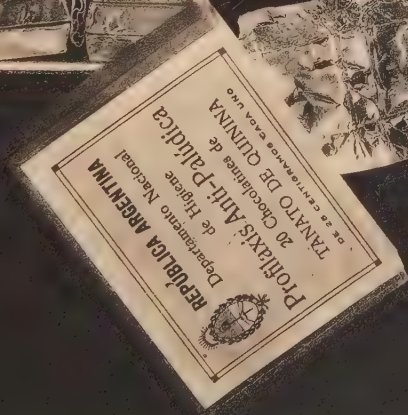
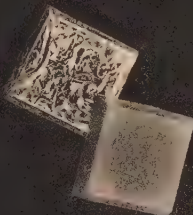


For children chocolate tablets with quinine tannate are often used, which they take without any difficulty.



Republica Argentina
Departamento Nacional de Higiene,
Chocolatines de tanato de
Quinina.

Instrucciones.
Estos preparados, que distribuye el Departamento Nacional de Higiene contienen verdaderos chocolatines de tanato de quinina *) en cada uno.
A los niños de uno ó dos años de edad debe



THE TREATMENT OF VARICES BY MEANS OF INTRA-VARICOSE INJECTIONS OF QUININE

(LE TRAITEMENT DES VARICES PAR LES INJECTIONS
INTRAVARIQUEUSES DE QUININE)

BY

A. MATHIEU, M.D., Marseille, France

Report of the Medical Committee of Bouches-du-Rhône, February 2, 1923

MATHIEU reports on six cases treated with injections of quinine bihydrochloride eulogized with so much reason by Genevrier. All six were cases of varicose veins of long standing with ulcers and varicose eczema.

All the cases were cured by two or three series of intra-varicose injections. Frequently Trendelenberg's sign became negative.

It was found in several cases that the cicatrisation of the ulcers proceeded rapidly, without interfering with the usual occupation of the patient, and in no instance was there any formation of scab, or appreciable pain at the point of injection.

On some few rare occasions only was a slight feeling of numbness of the limb experienced.

(Presse médicale, Paris, March 17, 1923, N. 22, p. 262)

CINCHONA DERIVATIVES IN THE TREATMENT OF HEART DISORDERS

Read before the Section on Practice of Medicine at the Seventy-Fourth
Annual Session of the American Medical Association,
San Francisco, June 1923

BY

K. F. WENCKEBACH, Vienna, Austria

QUININ has been used in heart treatment for a long time, certainly for more than sixty years. I must confess that I have not had time in these last years to look up the history of quinin as a heart drug, but I have heard that *Ludwig Traube*, the most outstanding man in experimental work in connection with clinical findings, added quinin to digitalis to prevent or relieve the disagreeable action of this drug on the stomach. I do not know whether this is true or not, but it is so related. Among the older generation of clinicians there was a good number, and I knew some of them, who nearly always gave digitalis in combination with quinin. On being asked why they did it, they could not give me an exact reason for it; but they found that digitalis was better supported with quinin and that they could give larger doses without getting disagreeable symptoms. One of them said that not only he but also his patients were very much satisfied with this form of treatment, so why should he not give this combination?

My objection to quinin in heart disease was that it had been shown by *Santesson* and by *Stokvis* to be a heart-paralyzing drug. Digitalis in toxic doses brings the heart to a standstill in systole; large doses of quinin however, bring

the heart to a standstill in diastole, and in smaller doses lead to a definite depression of the strength of the heart beat. This was the reason I did not wish to give quinin in cases of heart failure or any other bad condition of the heart. There I was wrong. We can never tell from the pharmacologic action of the drug how it will work at the bedside; for instance, we should never forget that the action of digitalis also on the heart is mainly and primarily a depressing action on the functions of heart muscles, at least as far as its vagus action is concerned, and still digitalis is the most powerful and most brilliant of all heart drugs. That we should not avoid giving drugs that have been found to be useful at the bedside on account of theoretical arguments only is shown in the following case:

In 1912, a patient presented himself in my office wishing to get rid of his attacks of auricular fibrillation. He knew that this was the so-called perpetual or complete arrhythmia and that his attacks ceased for the most part spontaneously after from two to fourteen days. He was a stout man, aged about 50, able to do a good deal of bodily exercise and even during the attack to walk for four or five hours. From this fact it was clear that the efficiency of his heart and circulation was only slightly diminished by the attack. He did not feel great discomfort during the attack but, as he said, being a Dutch merchant, used to good order in his affairs, he would like to have good order in his heart business also and asked why there were heart specialists if they could not abolish this very disagreeable phenomenon. On my telling him that I could promise him nothing, he told me that he knew himself how to get rid of his attacks, and as I did not believe him he promised to come back the next morning

with a regular pulse, and he did. It happens that quinin in many countries, especially in countries where there is a good deal of malaria, is a sort of drug for everything, just as one takes acetylsalicylic acid today if one does not feel well or is afraid of having taken cold. Occasionally, taking the drug during an attack of fibrillation, the patient found that the attack was stopped within from twenty to twenty-five minutes, and later he found that a gram of quinin regularly abolished his irregularity.

I was greatly struck by this fact, and afterward tried this sort of treatment in many cases of auricular fibrillation. My success was disappointing, in that quinin abolished auricular fibrillation in only a few cases and in those cases only when the onset of this form was quite recent, never when it was of several years' duration. At the same time, I found that even in those cases in which auricular fibrillation was not abolished, the drug had a marked soothing action on the often terrific rate of the ventricle. I received the impression that here the depressing, paralyzing action of the drug had a very favorable effect on the hyperactivity (hyperkinesis) of the heart. This made me try this form of treatment in other forms of arrhythmia due to some form of hyperkinesis also.

The first arrhythmia in which I had complete success with small doses of quinin (from 0.3 to 0.4 gm.) was extrasystole. It is well known that until that time we had no generally satisfying drug or method of treatment of this very common and innocuous, but at the same time very disagreeable, form of arrhythmia. For over fifty years I had been trying all of the drugs from which one might expect to have a quieting influence on the heart. Apart from digitalis in very small doses, which may work wonderfully in some exceptional

cases, there was only one drug which, I found unexpectedly, had a good influence on some of my patients, viz., strychnin. The first case which gave me proof of this favorable action of strychnin on extrasystole was that of a man with a very serious insufficiency of the aortic valves. His heart was in a very bad condition, and the man knew that he had only a short time to live. He bore his condition very well, but there was one thing which made life unendurable to him, namely, periods of extrasystole. The extraordinarily strong pulse wave, following the compensatory pause of the extrasystole, made him feel so utterly miserable that he asked energetically for relief. I gave him strychnin, which has been given in other countries for many years in cases of heart failure. In doses of from 2 to 3 mg. daily, this drug helped him as soon as extrasystole came on, and the favorable effect was not lost until the end. I have found strychnin in these small doses helpful in cases of extrasystole in otherwise normal as well as in diseased hearts, but very often it did not act strongly enough, or it lost its action very soon. In these last cases I tried the combination of quinin and strychnin and found that this form of treatment had complete success in the great majority of my cases. I have given from 0.3 to 0.4 gm. of quinin daily, plus 2 or 3 mg. of strychnin through periods of ten days. My experience with this treatment since the year 1915 has been so favorable that I am convinced that whoever will try it will come to the same conclusion.

After seeing this favorable effect, I thought it wise to try quinin in other forms of hyperactivity of the heart. Quinin being a depressing drug, we have to be very careful in cases of damaged heart muscle or real heart failure; we should

never imagine that quinin could be a heart stimulant. Keeping this in mind, I have found that quinin treatment has its greatest use in conditions in which an abnormal rhythm starts in the auricle or the atrioventricular node, or the ventricle interferes with the normal pacemaker of the heart. I have found it useful in all different forms of extrasystole; and, to some extent, in the different forms of paroxysmal tachycardia, but also in cases of marked so-called sinus arrhythmia starting in the normal pacemaker itself, quinin may act beneficially. In those forms of tachycardia, especially, found so frequently in adolescence, in nervous, rapidly grown-up young people, quinin, especially in combination with strychnin with its marked vasomotor influence, may be of great help. This is of the greater importance, because these tachycardias, certainly of central nervous origin, are very difficult to treat successfully. Long administration of small doses of digitalis sometimes has a favorable effect, but not at all in a really satisfactory way. The combination of quinin and strychnin stabilizes the heart action so quickly, and the young patients are themselves so much relieved, that after a short time it was possible to start the most important and causative treatment, viz., mental and muscular training.

Favorable effects may be seen in other typical hyperactivity of the heart: In exophthalmic goiter and other forms of hyperthyroidism, not only does the heart beat too quickly, but also the energy of every systole is much increased, as if under the influence of constant stimulation of the accelerator nerves. Quinin in doses of from 0.4 to 0.5 gm. has a decidedly quieting influence on the heart quite apart from whether there is auricular fibrillation or not. The patient himself is the first to notice this favorable effect.

In view of all these beneficial effects, it was to be wondered that quinin was active in so few cases of auricular fibrillation. Here *Walter Frey's* experiments were illuminating. Trying out the different derivatives of cinchona, he found that quinidin is much more powerful in abolishing auricular fibrillation than quinin. The difference between the two seemstobemerely quantitative. We found that by giving much larger doses of quinin we could get the same effect as by giving smaller doses of quinidin; but, on the other hand, in some cases of long-standing periods of extrasystole, quinidin had the full effect where quinin had been given for a long time without giving more than slight relief. Certainly, the introduction of quinidin as a form of quinin treatment has proved to be of the greatest advantage. The „dramatic” transition of long-standing complete arrhythmia into a perfectly normal mechanism of the heart has made a great impression on physicians over all of the world and made, at least, this form of quinin treatment quite popular.

Summarizing my own experience and the work done by others, I may say that quinidin has its greatest success in those cases in which there is not much wrong with the heart, in which fibrillation has been present for not too long a time or is showing itself in attacks as a special form of paroxysmal tachycardia. When auricular fibrillation is the only abnormal phenomenon of the heart, the disappearance of this disagreeable form of disturbance of the heart mechanism may be a complete cure, freeing the patient not only from his subjective symptoms but at the same time of the suspicion of having a myocarditis, or, at least, of some bad condition of the heart muscles. On the other hand, in cases in which fibrillation is only a part of the morbid condition, when valvular disease

or pathologic changes in the heart muscle are the chief features of the disease, the abolishing of fibrillation will give only partial relief. In such cases we should never forget that all cinchona derivatives are depressing drugs and should not be given in too large quantities. Generally speaking, real heart failure asks for digitalis, and it may be necessary to avoid quinidin until the condition of the heart is much better. I, myself, am giving the combination of digitalis and quinin from the very beginning, especially when there is a very rapid and irregular action of the heart, doing, as a matter of fact, what old clinicians did a great many years ago. To avoid an unfavorable effect of quinidin, one should try to find out whether auricular fibrillation plays an important rôle in the development of the disturbance of the circulation; with a slow ventricular rate there will not be much use for quinidin, and when there is a dangerous condition of heart muscle failure it may even do harm. Limiting quinidin treatment to cases in which fibrillation is a real factor of importance or the only symptom, one may see many beautiful cures and avoid the accidents mentioned in the literature. Certainly the last word in this important therapeutic matter has not been spoken, and careful observation of every patient under treatment will be necessary before we shall know all we wish to know about quinidin treatment in auricular fibrillation.

The great impression that quinidin treatment made on the medical profession is certainly due to the fact that its favorable effect shows itself suddenly by the transition of long-standing irregularity into normal rhythm after the administration of the drug. It is this sudden effect that gives absolute proof of its activity. Would it not be possible to get the same form of convincing proof for the action of quinin in those

other forms of irregularity of which I have been speaking rather enthusiastically? This proof has been provided by *Winterberg*. He found in my clinic that intravenous injection of quinin (not quinidin) may stop an attack of paroxysmal tachycardia in many cases, and sometimes so quickly that he had to keep his electrocardiograph running in order not to miss the interesting moment of transition from the pathologic to the normal rhythm. In a few specimens of tracings which I am able to show, the sudden stopping of the attack was obtained by the injection of not more than 0.5 or 0.75 gm. of quinin, a dose perfectly supported by all our patients and much smaller than the doses injected intravenously in cases of long-standing or severe tropical malaria. The patient himself has the curious sensation of a heat wave passing through his body, and no other disagreeable effect; only rarely did we have to deal with depressing actions of quinin on the tonus of the vessel wall, showing itself in a fall of blood pressure and sometimes in syncope, easily relieved by some stimulants. The same favorable effects of the intravenous injection are shown in one of these tracings from a case of extrasystoles coming on in long series, that resisted quinin treatment by mouth, so that proof of the favorable action of quinin on extrasystole, so evident but not showing itself so immediately in treatment by mouth, is given in a way absolutely equal to any form of experiment.

It would take too much time if I should try to deal broadly and deeply with the question of the analysis of the action of quinin on the heart muscle. This question requires a great deal more experimental work: certainly, it is not sufficient to say simply that quinin lengthens the refractory period of the heart. We must investigate the effect of quinidin on

every single function of the heart muscle and distinguish between its primary and its secondary effect in the way *Engelmann* taught us. What this means may be exemplified by the well-known fact that digitalis, which lengthens the conduction time, may have a favorable effect even in cases in which there is a lack of conductivity. This favorable effect is due to the fact that digitalis at the same time both slows the heart and provides it with a longer time for restoring its various functions.

Before leaving this subject I want to say a few words about another influence of quinin bodies which may prove useful in the treatment of cardiovascular conditions: the syncope just mentioned is generally and probably rightly ascribed to vasodilatation, not so much to depressing action on the heart. Some clinical observations have shown that in so-called vascular crises (sudden spasm, i. e., hyperkinesis of the walls of the smaller arteries) quinin may stop the spasm and so relieve the patient of his symptoms. *Winterberg* found that, in some cases of anginal pain accompanied by sudden and very important rise of blood pressure, intravenous injections of 0.5 gm. of quinin may stop the attack at once and completely so that not only the pain but also the enormous rise in blood pressure is abolished. *Winterberg* has described the details of this interesting case. I simply want to point out that the problem of quinin in the treatment of heart disease and cardiovascular conditions covers a much larger area than the question of quinin and auricular fibrillation only, and that the action of this drug on the arterial system and its rôle played on the circulation in general should be studied carefully.

That quinin must be of the greatest importance in the

treatment of such conditions has been perfectly known to the old clinicians. The Viennese clinician *Oppolzer*, in his lectures on the treatment of internal diseases (1872), begins his chapter on the treatment of heart diseases with the words: "The best and most powerful factors in dealing with heart patients are three: rest, digitalis and quinin." Curiously enough, all of us had forgotten about quinin. Certainly, we did not know exactly in which cases it should be given, and we had insufficient experimental evidence about its action only, viz., that it is a heart-paralyzing drug. I, myself, avoided quinin only on this theoretical reasoning. The facts now known teach us that certainly the last word in therapeutics has to be said at the bedside—but, at the same time, that experimental evidence and careful analysis of the action of the drug will give us a clearer insight into the important question, in which cases it should be avoided. I think all will see that the reintroduction of quinin into therapeutics not only is an important acquisition in the treatment of heart disease but at the same time gives us a useful and beautiful instance of the cooperation of clinical and experimental investigation.

(Journal of the American Medical Association, Chicago, Aug. 11, 1923, pp. 472—474)

QUININE AND UREA HYDROCHLORIDE AS A LOCAL ANAESTHETIC

BY

J. W. VAN DER SPEK, M.D., Bloemendaal, Holland

HERZIG (New-York Medical Journal of March 1914, p. 529) publishes his results obtained by the use of quinine and urea hydrochloride as a local anaesthetic in nose and throat operations. *J. F. Saphir* (see below) and *Prof. Dumont* of Berne (*Correspondenzblatt für Schweizer Aerzte*, April 1918, No. 14: *Ein Lokal-anaestheticum von ungewöhnlicher Wirkungsdauer*) emphasize in the same way its very satisfactory results.

Quinine and urea hydrochloride satisfies — vide *Herzig* — a long felt want, being non-toxic, anti-hæmorrhagic and a perfect anaesthetic. He uses a 4% solution mixed with 1% of boric acid.

After the usual preparations (clearing the bowels, and no meal four hours before operation), he injects 10 minims into the anterior pillar of the fauces high up, and 10 minims into the posterior pillar low down in cases of tonsil resection. If injection in the posterior pillar owing to very large tonsils is not possible, only one injection is made.

In cases of adenoids he uses a 50% solution and swabs this on with a post-nasal applicator. After 15 minutes the anaesthesia is nearly as complete as that after an injection.

Herzig operated in 390 cases, 150 were adenoids, and 240 adenoids with enlarged tonsils.

Of these 240, over one third were in adults over 16 years. In six cases the lower half of the uvula was resected. In these cases the injection was made at the junction of the uvula and soft palate.

No patient had apparent pain. In none of these cases was there any hæmorrhage 5 minutes after the operation, and no post-operative hæmorrhage.

The patients complained of soreness of the throat after operation, although anaesthesia was present.

There is no fear of edema spreading to the glottis.

One or two days after the operation there is an edema which spreads from one anterior pillar to the other, involving soft palate and uvula. This disappears in 3—10 days. Sucking of ice gives a marked relief.

Sometimes a membrane forms over the site of the injection. This disappears also in 2—10 days and is due to the urea. This membrane is no sign of infection.

The quinine is the anaesthetic; the urea by means of its irritant properties causes the edema, which acts as a hæmostatic.

Patients must gargle with equal parts of hydrogen peroxyde and tepid water every 3 hours and abstain from solid food for 36 hours. In case of much suffering from soreness cold compresses are applied externally.

Concluding, the author emphasizes the advantages of quinine and urea hydrochloride over cocaine in that it is non-toxic and hæmostatic.

J. F. Saphir (New-York Medical Journal, Dec. 22, 1917) strongly recommends the use of the combination, quinine

and urea hydrochloride, as "the ideal local anaesthetic for rectal operations."

In rectal operations where a general anaesthetic cannot be given on account of lung, kidney or heart trouble, or when patients are thoroughly exsanguinated, a local anaesthetic is indicated. *Saphir* used a solution of quinine and urea hydrochloride in over 2000 cases with most gratifying results.

This solution is non-irritating and produces an exudation of fibrin. The duration of the local anaesthesia, which lasts from 3 to 10 days, the amount of exudated fibrin, and the more or less rapid production of the anaesthesia, depends upon the strength of the solution.

One % and 0.5% solutions give complete and immediate anaesthesia without pain during injection, and within one or two minutes, induration, with the production of fibrin produced.

The complete sensation in the part involved is not restored until two weeks, when using the 1% solution, and for 10 days with the 0.5% solution.

A 0.25% solution produces anaesthesia after a few minutes, a 0.125% after 10—15 minutes.

The advantages are: 1. The non-toxicity even when given in large quantities. 2. The prolonged anaesthetic effect, giving a sufficient length of time in which a wound may heal. 3. The production of fibrin which compresses the walls of the blood-vessels, and acts as an excellent haemostatic. This effect lasts from 4 to 10 days and is sufficient to permit healing by granulation, thereby minimizing the danger of post-operative hæmorrhages. 4. The solution can be easily sterilized.

Saphir points to the danger of hæmorrhage when using

adrenalin as soon as the effect of that drug wears off, and remarks on the strange fact that cocaine solutions, even weak ones, when used in rectal local anaesthesia, produce toxic symptoms more rapidly and frequently than when administered in any other part of the body.

An objection raised against the use of quinine and urea hydrochloride, is delayed healing or inability to secure primary union. This can be easily overcome by using only weak solutions, 0.5 % for general, and 0.3 % for skin tissue.

The injection can be made with a glass or metal syringe. A fine needle with a sharp point is necessary.

The solution must be freshly prepared and slowly injected, taking care that nothing escapes from the injected tissues.

Preparing the patient with strong cathartics is not advisable. An enema 12 hours before operation is sufficient. After washing the parts with water and green soap, the rectum is swabbed out with cotton moistened in a weak lysol solution.

Saphir now describes various rectal operations, in which he generally uses a 0.5 % solution of quinine and urea hydrochloride for local anaesthesia.

In cases of ulcerated internal hæmorrhoids which bleed profusely, relief was obtained by injecting a 5 or 10 % solution into the hæmorrhoids. The bleeding stops, and the ulcerations heal.

Saphir never gives opium; motion of the bowels after operation is allowed. He strongly condemns the dilatation of the sphincter and the insertion of a stout walled rubber tube rolled in iodoform gauze.

Schepelmann (*Therapie der Gegenwart*, Dec. 1911: *Chinin als Local-Anaestheticum*), recommends the combin-

ation of quinine and antipyrin. The burning pain immediately after the injection of a quinine solution can be prevented by adding antipyrin. The formula is:

Quinine hydrochlor.		0,3 grams
Antipyrin		0,3 „
Aq. dest. ad		10 „

Henry Hansen (Hospitalstidende January 29, 1923, p. 48) arrives at the same conclusions about quinine and urea hydrochloride. The advantages are: easy to sterilize, non-toxic, hæmostatic, long duration of anaesthesia, cheap and equal to cocaine.

There is no doubt that in cases of granulating wounds (rectal operations) an anaesthetic with a prolonged effect, must be very useful.

ON QUININE THERAPY IN ABORTUS FEBRILIS

(UEBER CHININTHERAPIE BEIM ABORTUS FEBRILIS)

BY

E. HENRARD, M. D.

Assistant to the University Clinic for Women, Königsberg, Prussia

ALTHOUGH the dispute regarding the most suitable treatment for febrile abortus is still not definitely settled the disciples of the so-called "conservative" therapy, who refrain from active interference in cases where infection is present, because of the danger of its mechanical spread are on the increase. This, the principal standpoint, remains unaffected by the opinion — also maintained by the "non-activists" — that a complete clearance from the uterus of its infectious contents *as soon as possible* is the greatest desideratum and is the most favourable factor as regards convalescence and complete recovery. This view relies in the first place on the experience that uncomplicated febrile abortions, after spontaneous expulsion, promptly decrease in fever and permanently in the majority of cases.

Out of material selected in our clinic from 24 uncomplicated febrile abortions, which ended without our interference spontaneously, 21, that is to say 88%, showed an immediate and lasting decrease of temperature to normal after the contents of the uterus had been expelled — although 12 of them (50%) were admittedly caused criminally. The 3 exceptions — all criminal abortions — were in 2 of them succeeded by a resorptive fever which ended 24 hours after abortion, and in one by a parametritis.

The decrease of temperature in these spontaneous abortions being without doubt due to the removal of the source of infection, it seemed indicated — when abstaining from

active interference — in cases which dragged on for days, and which showed little tendency to spontaneous expulsion, to try a form of *medicamental* therapy, in order to ensure as rapid as possible a termination to *each* abortion.

I would therefore like to report on a treatment which is indeed not new, but nevertheless which is not well enough known, and which — according to our clinical experience — represents a gratifying improvement in the treatment of abortus by the conservative method, since it stimulates and assists in many cases the natural defensive forces, which are effective in a spontaneous expulsion of the abortus and improves without any apparent harmful effect the health of the patients, rendering them fit to work again: — it is the use of quinine.

Its importance in labour has been the subject of considerable discussion by obstetricians. The avowed opinion of numerous authors is opposed to the standpoint of almost as many specialists again who question the effect of quinine, or at least regard it as very uncertain (See *Halban & Koehler*, Wiener Klin. Wochenschrift 1917, No. 16). Critically we have to remark that this appreciation was based on its early use which was almost entirely *per os* and on a more or less uncertain dosage. Since however, in 1917, *Halban & Koehler* introduced the *Bacelli intravenous* quinine injection (which was successful in malarial treatment without any undesirable local or general by-effects) into obstetrics, and proved it to be “an outstanding aid in labour”, on this method, just as it is when given intramuscularly, the value of quinine should no longer be in doubt. It must be remembered that quinine only acts on a uterus “commencing labour”, and that one cannot induce a birth or provoke an abortion

with quinine in therapeutic doses. Bearing this in mind, we have administered quinine in our Clinic in numerous cases of labour weakness at birth with good results.

Its application — at least experimental — in the new form of *injections* in abortus imminens, abortus “in course”, and abortus incompletus, was obvious, and has been also tried by *Halban & Koehler* themselves. With a total of 16 cases of threatening abortus or abortus in course of 2-6 months, 15 positive results were obtained, and one negative — i.e. in 94% an absolute success. The abortus incompletus proved to be far more unfavourable as out of 12 cases only 3 cases (25%) reacted with spontaneous expulsion of the retained placenta. *Franz* (*Wiener Klin. Woch.* 1917, No. 34) obtained similar results. In his cases, though few, quinine injections were used in 6 cases of abortus in course, 5 responded (83%) and one failed to respond and 3 cases of abortus incompletus failed completely. Experiments made by *Werner* (*Mon. f. Geb. u. Gyn.*, Vol. 48 and *Ztbl. f. Gyn.*, Vol. 43) with a combined intravenous and intramuscular administration each of 0.5 gram quinine hydrochlor. of 5% gave the following result: “In miscarriages the embryo is always expelled at any stage and at any time, but not always the attachments. *Abortion remnants* are not expelled. *Hintzelmann* (*Mon. f. Geb.*, vol. 52) recommends intravenous 1.0 gram quinine and urethane, especially in febrile abortion, in order to reduce mechanical interference to a minimum.

For some time past we have ourselves given quinine systematically for all febrile abortions in the most varying stages, including retention of the placenta, when labour pains were absent or very weak. In order to produce as intensive an action as possible, each patient received the quinine “in three forms”, viz. 2 c.c. each of a 25% solution quinine bihydrochlor. (that is each 0.5 gram) intravenously and intramuscularly and also 2 tablets of 0.25 gram quinine hydrochlor. per os.

We give now the results obtained with this method in 92 cases, i.e. 45 abortions in course (that is foetus and placenta in utero),

40 abortus incompleti with retention of the whole placenta,

7 “ “ with retention of placental attachments and remnants.

Generally, it may be said that in all cases the relatively high dose of about 1.5 grams quinine was well borne. Many patients complained of slight vertigo, rush of blood to the head, deafness, but these symptoms of slight "cinchonism", which practically never were a source of serious trouble to the women, rapidly disappeared. One patient only suffered from deafness for a whole day. Vomiting and cardiac sensations were never encountered by us. Naturally great care had to be taken to ensure a *very slow and gradual injection into the vein of the arm*. The statement by Halban & Koehler that the women "experience the sensation of profuse bleeding from the genitals", nearly always at the moment or shortly after the intravenous injection (notwithstanding this cannot be found objectively) has often been confirmed.

Local tissue reactions, especially abscesses and necrosis of the skin at the site of injection which have been observed by many authors, we did not find. Perhaps we are indebted for this to a slight "prophylaxis" which we adopt, viz. after each intravenous injection we lay a swab saturated with alcohol on the point of injection and put a small bandage round it, a method which has also proved successful after intravenous injections of Argochrom and similar remedies. As a site for *intramuscular* injection there is chosen, according to Latzko (Ztbl. 1917), perhaps better than the glutaei, the muscles on the outside of the thighs, as injections into the gluteal region, not made deeply enough, do not reach the muscles, but are only deposited in the fat.

It is of course well known that tablets are better swallowed unchewn on account of their bitter taste.

Now to come to the results of the treatment separately. Of the 45 cases of febrile abortus "in course" 36 (= 80%) were *entirely*

completed, that is to say, in four fifth's of all these cases, the administration of quinine led to the spontaneous expulsion of foetus and placenta. 9 cases ($= 20\%$) were regarded as negative. After quinine, in five of them only the foetus was delivered, the placenta being removed digitally, because of the profuse haemorrhage — to this I will revert. In three others of the "negative" cases, a considerable enlargement of the cervical canal followed, the final effect being only produced by Pituglandol or Physormon. In only one case was quinine absolutely without effect in a 4 months' abortion, even after the "triple" dose of quinine has been repeated after twice 24 hours.

The 40 cases of abortus febrilis incompletus with retention of the whole placenta were completed by quinine with spontaneous expulsion in 21 cases ($= 52\%$), whereas in 19 cases ($= 48\%$) digital clearance was necessary; (in 5 cases, owing to a profuse haemorrhage).

In 7 retentions of more or less large pieces of placenta, quinine caused the complete expulsion only once, the remaining 6 had to be cleared digitally (after the fall of the temperature).

It is worthy of note that with quinine in almost all cases the clearance which had been necessary has been very slight and pain-saving for the patient, without further instrumental dilatation, as the "quinine labour-pains" — to express myself shortly — enlarged the cervical canal very adequately, and also induced a loosening of the placenta.

It should also be mentioned that of the cases regarded as positive, in one third the use of the Credé or Hoening method was necessary to remove the detached placenta. It is a good plan therefore to get the women to *empty the bladder before injecting the quinine*.

As we have already stated there were, in all, 10 cases among the 92 under observation — therefore no small percentage — which displayed marked *haemorrhage* after the injection of quinine and this was the sign for active interference. To explain these haemorrhages, as does *Mäuren* (Deut. Med. Woch. 1917) as due to paralysis of the uterine muscle owing to too large doses of quinine, is not really correct, as often the labour pains continued and there was never very profuse haemorrhage in cases where small portions of placenta were retained. They occur more frequently — as one can often observe when a removal is necessary — by reason of the partial detachment of the

placenta and the consequent defective retraction of the wall of the uterus. During our observations we had the experience that such haemorrhages in abortion seldom become unbearable. In the last two cases of this kind 1.0 gram Secacornin intramuscularly had a very prompt effect: the bleeding ceased and the placenta was soon expelled spontaneously. Hence active interference was unnecessary. It goes without saying, of course, that if such treatment were unsuccessful one would not let haemorrhage persist to a *pronounced* degree, but if need be, interfere actively. As regards the limit of waiting we regard a loss of blood of 800—1000 grams as decisive.

Furthermore a really typical observation was that the quinine itself did not cause the lowering of the fever, but that the induced evacuation of the uterus by the quinine was the cause; often patients who had had quinine remained febrile, and only when the placenta was expelled did the temperature drop immediately to normal. It remains open to question whether the quinine — as *Scott & Bertrand* state regarding the course of the confinement of women treated intra partum with quinine — exercises any influence on the favourable progress of the general condition. But it is a fact that in 8 cases only a slight endometritis, in 2 a parametritis, followed the abortion, whereas all the remaining patients showed a normal condition of the genitals about 8 days after the completion of the abortion.

If I therefore shortly tabulate my experiences the result is:

1. In febrile abortus quinine treatment is to be recommended very much in all stages. Its use in "triple form" (i.e. quin. bihydrochlor. 25% 2 c.c. both intravenously and intramuscularly, as well as 2 tablets of quinine hydrochlor. each 0.25 gram per os) has given us good results. Four fifths of all the cases of febrile abortions actually "in course" and about half of the cases of placental retention were cleared spontaneously by this method and active interference was unnecessary.
2. Quinine failed in cases of retention of small remnants of placenta.

3. In such cases where quinine failed, the effect produced by its loosening of the placenta was valuable, as dilatation of the cervical canal was thereby rendered unnecessary, and the manual expulsion of the placenta was very simple and pain-saving for the patient.
4. Care must be exercised in regard to profuse haemorrhage after the use of quinine. Before a removal, deemed necessary by reason of the haemorrhage, the effect of 1,0 gram Secacornin intramuscularly should be tried.

(*Monatsschrift für Geburtshilfe und Gynäkologie*, Berlin, Vol. LXIII, No. 1, May 1923, pp. 19—24)

THE CONSERVATIVE TREATMENT OF ABORTION

(DIE KONSERVATIVE BEHANDLUNG DES ABORTUS)

BY

Prof. Josef LOVRICH, M. D.

Director of the Training School for midwives, Budapest, Hungary

IN 1913, I commenced experiments in conservative methods for the treatment of abortion and have convinced myself of their efficacy. Active treatment, in a great number of infectious cases, leads to grave complications, hurts and even death. I have given lengthy consideration to the elaboration of a method, which may be utilisable even by the general practitioner and would be less dangerous than active treatment.

In this connection I have borne in mind the fact that we still cannot decide whether the infection spreads only in the uterine cavity or whether it has become para-uterine already.

In cases where there are absolutely no clinical signs of infection, we have observed when treating them actively, extremely serious complications. Daily observation teaches that the induction of an abortion by inexperienced persons, who unfortunately nearly always remain unknown, is accompanied by severe fever and shivering in which condition the patients require not merely the help of a doctor but admission to hospital. Such cases often give the physician disagreeable surprises. Further, when there is already infection, whether with or without clinical signs, and the physician commences active interference in the infectious area or the surrounding parts, extension of the infection is almost inevitable and there

are incessant signs of sepsis, pyaemia or even the fatal peritonitis. Often the physician in charge of the cases is considered responsible for this unhappy issue which has, however, been caused by others, merely for the reason that he was the last to undertake treatment.

Consequent upon these conclusions, I reported in 1914, for the first time to the Gynaecological Section of Budapest, on the conservative treatment of abortion. Not having an abundance of material I in the course of 9 years, treated 324 abortions exclusively by the conservative method. Including even the most desperate cases, I had to record only 3 cases of death. If I now add to this the 120 cases of artificial abortion during these 9 years, in which cases we, on account of severe illness always induced the abortion by puncturing the membranes and than left it the forces of nature to act, without ever losing a case, then I can — with a clear conscience — recommend the conservative method to the practising medical man.

Our method is as follows :

In abortion (*incipiens* or *incompletus*) we give quinine; in the first 24 hours not more than 1 gram. Following *Herff's* method, we give later quinine and veronal in equal proportions in $\frac{1}{2}$ gram doses half hourly. Or else we divide 1 gram into 5 powders, with an equal quantity of veronal in doses of 0.2 gram which we also administer every half hour. Sometimes we also give initially a dose of 0.4 gram and later half hourly doses of 0.2 gram. When the quinine commences to cause pains, we give pituitary extract.

We use only the most reliable preparations of hypophysis (Hungarian glanduitrin, pituitrin, or pituglandol). When a more profuse haemorrhage commences, then we give at

intervals of 10—15 minutes, 3—4 injections of hypophysis extract. In this connection we have to report that when the pregnancy is undisturbed, neither the influence of the quinine nor the hypophysis — alone or together — induces labour pains. We have had evil experiences with a bad “war” quality both of quinine and hypophysis extract.

Our statistics are:

Number of abortions.	324
Primiparae	83 (about 25 %))
Pluriparae	241 („ 75 %))
1st month	21 (6.48 %)
2nd „	80 (24.69 %)
3rd „	66 (20.37 %)
4th „	54 (16.66 %)
5th „	47 (14.50 %)
6th „	41 (12.65 %)
7th „	15 (4.63 %)
Incipiens	212 (65.43 %)
Incompletus	112 (34.56 %)
When admitted to hospital highly feverish, with	
ichorous discharge	26 (8.02 %)
Feverish	34 (10.49 %)
Subfebrile (99°—100°)	60 (18.52 %)
Free from fever, when admitted to hospital. . .	192 (59.26 %)
Free from fever, but having had fever before. . .	12 (3.70 %)
Advised as certainly criminal	5 (1.54 %)
We gave quinine in	170 (52.47 %)

The abortion was completed in medium 38 hours after the initial dose of quinine.

0.5 gram quinine was given in	4 cases (2.35 %)
1.0 „ „ „ „ „	70 „ (41.20 %)
1.5 grams „ „ „ „ „	26 „ (15.30 %)
2.0 „ „ „ „ „	37 „ (21.76 %)

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3.0 grams quinine was given in	15 cases (8.82 %)
4.0 " " " " "	7 " (4.12 %)
4.5 " " " " "	1 case (0.58 %)
5.0 " " " " "	4 cases (2.35 %)
6.0 " " " " "	4 " (2.35 %)
10.0 " " " " "	1 case (0.58 %)
12.0 " " " " "	1 " (0.58 %)

Total in 170 cases.

<i>Quineonal</i> was given in	66 cases (20.37 %)
(smallest dose 0.2 gram, largest dose 4.0 grams)	
<i>Glanduitrine</i>	122 " (37.65 %)
(smallest dose 1 c.c., largest 29 c.c.)	
<i>Pituitrine</i>	23 " (7.13 %)
(smallest dose 1 c.c., largest 11 c.c.)	
<i>Quinine</i> (alone)	51 " (15.74 %)
(the <i>medium</i> duration of the abortion was 18 hours)	
<i>Glanduitrine</i> (alone)	8 " (2.46 %)
(completion of abortion in 12 hours, in me- dium 1.5 c.c.)	
<i>Pituitrine</i> (alone)	1 case (0.31 %)
(the dose was 1 c.c.)	
<i>Pituglandol</i> (alone)	2 cases (0.62 %)
(was completed within 24 hours).	
<i>Hypoglandine</i> (alone).	1 case (0.31 %)
<i>Quinine</i> + <i>Glanduitrine</i>	77 cases (23.77 %)
<i>Quinine</i> + <i>Pituitrine</i>	20 " (6.17 %)
<i>Quinine</i> + <i>Pituglandol</i>	6 " (1.85 %)
<i>Quinine</i> + <i>Hypoglandine</i>	11 " (3.39 %)
<i>Spontaneous termination</i> , out of 324 abortions, in which we did not give anything, in . . .	64 " (19.70 %)

Exceptionally good results were experienced with patients admitted to hospital in a febrile condition. In 2—3 days the

fever disappeared as well as the bad discharge — the pulse falling to normal. An indescribable feeling of relief and confidence is experienced when the abortion progresses normally without such complications as shivering or peritonitis. For those who desire to use active treatment when there is fever or a suspicion of infection, we desire to point out that we have still no definite clinical signs to prove the weak virulence of the infectious germs.

For myself I shall never forget the feeling of uncertainty which oppressed me in the Obstetric Clinic in regard to the many thousand patients treated actively, if a septic abortion was in question or even where there was a suspicion of infection. The chief advantage of the conservative method is that one cannot do any active damage with it. Its disadvantage however, is that by it, the course of the abortion is prolonged, and particularly the fact that the pregnant woman does not feel calm, so long as she is not altogether freed from her pregnancy. Thus we find not the doctor alone, but the women themselves the most serious opponents to the conservative treatment.

With this method of treatment I do not however, want to take action against authorities who by reason of their immense technique, foresight and experience know how to protect the patient from severe complications, and especially to avoid injuring them by the active method. The triumph of the conservative method is the good confinement. In 268 of our cases we had no fever (82.7 %). Febrile once in 18 cases (5.6 %), and prolonged fever 28 cases (8.64 %). Slight malaise was observed in 4 cases (1.23 %), severe illness in 3 cases (0.92 %). Of the fatal cases (0.9 %), one patient died after 9 days from pyaemia and one after 4 days of peritonitis.

In the latter case we had to resort to the active method because of haemorrhage. The third died also of peritonitis after 20 days.

I must emphasise that apart from one or two applications of tampons, and the one active treatment mentioned above, there was no other active interference. In abortions with haemorrhage active treatment is unnecessary, as such haemorrhage is caused by the loosening of the placenta and for its removal out of the womb hypophysis extract suffices.

(Münchener Medizinische Wochenschrift, October 5th, 1923, p. 1249)

THE RESULT OF TREATMENT OF ABORTION BY QUININE, GIVEN PER OS

(DIE ERGEBNISSE DER ABORTUSBEHANDLUNG
MIT CHININ BEI ORALER VERABREICHUNG)

BY

ROBERT POSCHACHER, M. D.

From the I. University Clinic for Women in Vienna

UNTIL about 18 months ago, treatment of abortion at the I. University Clinic for women was mostly operative. *Thaler* reported on this during the discussion on the lecture delivered by *Latzko* on "Abortion" at the meeting of the Vienna Gynaecological Society held on November 9th, 1920. *Mauthner*, who made a report on all cases from 1892 till 1919, comes to the conclusion that the most satisfactory method, in the clinic, for the treatment of febrile abortion is immediate removal in one turn.

For two years past we have, in every case of abortus incipiens and incompletus, whether febrile or afebrile — so long as a profuse haemorrhage has not indicated an immediate removal — tried treatment with quinine given per os. At the outset, I would like to say that there was no difference in the result of the treatment of febrile or afebrile cases and that is why a sub-division seems unnecessary. *From April 1st 1921 to April 1st 1923 we treated altogether 133 cases of abortion with quinine.*

During recent years according to *Halban*, *Koehler*, *Franz*, *Werner* and others, a large number of authors have used quinine in obstetric practice, and have reported on

their results with this treatment. Each author, however, discussed only a few cases with the exception of *Hintzelmann* (Hamburg) who reports on 67 cases of febrile abortion in which quinine was injected, and *Precechtel* (Prague) who gave quinine in 24 cases per os. According to the results achieved by *Franz* and *Katz* there appears to be no particular advantage in the treatment by injection over administration per os, a fact which we can also confirm, as the results obtained with our relatively large material display remarkable agreement with those reported by *Halban* and *Koehler* with their injection method.

Last year, in each case of abortion, if a somewhat severe haemorrhage did not call for active interference, we administered quinine, and we gave four 0,25 gram doses of quinine hydrochlor. or sulphate, at intervals of a quarter of an hour, in cachets. This treatment, if successful, usually operates in the first 24 hours, though in quite a number of cases we observed an effect after 24 hours or more. If there was no effect at all, a repetition of the doses of quinine was very rarely successful. If with quinine we achieved a spontaneous removal of the foetus alone, we mostly could not obtain a removal of the placenta with a new dose of quinine (accumulation of quinine in utero? *Joachimowitsch*, Gynaecological Congress Heidelberg, 1923). A remarkable difference is observed where there is still a foetus and a placenta in the uterus as opposed to cases of abortus incompletus. Whereas in the former cases (67) 55% showed a complete result, in 27% a partial — the expulsion of the embryo only, while the placenta had to be removed digitally — and only 18% were unsuccessful, we found that in abortus incompletus only 30% of the cases were successful, and with

less trouble when the whole placenta or at least large portions of it were still in the uterus.

The age of the pregnancy plays a part too, as in cases where the os uteri could already admit one or more fingers and the complete embryo was still in the uterus. In 23 of such cases where there was a pregnancy of over three months, we have not had to report a single failure. If we were compelled to undertake removal after a negative or a partial success, we could accomplish this digitally in 50% of the cases without, and in other cases, with but very little dilatation. The same advantage could be observed in cases of abortus incompletus, which we consider as negative cases. We were in a position, in 66%, to clear them digitally without previous dilatation.

In *conclusion* we can say as follows: the fact that quinine has an effect on a uterus ready for labour, to which attention has been drawn by *Franz* and *Katz*, has been confirmed in our experience. The further advanced the pregnancy and the abortion, and the more the cervical canal — and consequently the os uteri — is enlarged, the better the results obtained with quinine. In abortus incompletus, on the other hand, quinine is less active, the smaller the placental remnants in the uterus are, resp. the more the uterus has quieted down again.

In abortus incipiens we were successful with 82%, with abortus incompletus with 30%.

If no success at all or only a partial success is achieved with quinine, then at least, it effects an enlargement of the cervical canal or maintains the enlargement which already exists, thereby easing the removal, so that it can be performed in more than half of the cases completely without dilatation.

We have never been able to detect any injury caused by quinine; the well-known often undoubtedly annoying accessory effects, as tinnitus aurium, sensation of dulness in the head and deafness invariably soon passed off. The quinine was very seldom vomited, and then frequently only by patients with high temperatures. The duration of the delay is — on the average — 2 to 3 days longer than with the active method but only 8 of our 133 cases lasted longer than 10 days.

Taking into consideration the good results achieved and the simplicity of determining the dose — of particular importance for the country practitioner — I want to advise, as *Liepmann* says in the *Therapeutische Monatshefte* of the forceps: "No forceps is to be advised without a preliminary trial of pituglandol": *In every case of abortion, especially in feverish abortion there should be no removal without first of all trying the effect of quinine.*

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(Wiener Klinische Wochenschrift, Aug. 9, 1923, pp. 572—573)

THE ACTION OF QUININE ON PREGNANCY AND DELIVERY

(UEBER WIRKUNG DES CHININS AUF DIE
GRAVIDITÄT UND DEN GEBURTSAKT)

BY

M. SLARTSCHEFF, M.D., Sofia, Bulgaria

THE author, an experienced obstetrician, assembles his experiences on the subject and adds several personal remarks.

He divides the subject into four parts:

1. The action of quinine as a curative agent in pregnant women suffering from malaria.
2. Abortive action on the pregnant uterus, physiologically normal.
3. Quinine as an ecboic in cases where labour pains have not yet set in, as in intra-uterine death of child, loss of waters abortion, etc.
4. Quinine as a strengthener of pains in abortion and normal delivery.

Among other observations the author brings forward a personal one, referring to a 42 years old multipara, who getting malaria in the fourth month of pregnancy, took over 100 grams of quinine hypodermically and by the mouth, without any interruption of the pregnancy.

The author sums up his conclusions as follows:

1. Quinine taken in therapeutic doses, has no action on the gravid uterus and foetus as far as the interruption of pregnancy is concerned.

2. Quinine can be given to pregnant women without any risk, in the usual doses.
3. Abortion and premature delivery which may occur with pregnant women after absorption of quinine, is not due to the quinine, but to the strong increase of temperature in the malaria cases.
4. Quinine is the best prophylactic agent for continuation of pregnancy in malaria cases.
5. Quinine is very seldom an ecbolic.
6. Quinine often has a favourable action as strengthener of pains, but this action is not constant and cannot be foreseen.
7. It is not of practical use for facilitating the expulsion of the placenta after the delivery. There are other agents which are preferable for their quick and certain action.
(W. Mollow, Sofia, in *Archiv für Schiffs- und Tropen-Hygiene*, Vol. 27, 1923, No. I, pp. 46—47)

THE EFFECT OF QUININE ON THE ACUITY OF HEARING

QUININE in certain doses is well known to produce well-marked effects on the auditory apparatus, including a degree of deafness and tinnitus. The question arises whether the tinnitus has any appreciable effect on the acuity of hearing at any and all pitches. The disadvantages of the watch-tick as a test for minimum audibility are obvious, nor is the tuning-fork free from error. A. G. Pohlman and F. W. Kranz (Proc. Soc. for Biol. and Med., vol. XX, 1922) describe their method for determining minimum audibility as a function of pitch, pointing out, however, the extreme importance, in work on minimum audibility, of bearing in mind the variable factor of attention. It was found that a 25 gr. dose of quinine sulphate taken in 5 gr. gelatin capsules at hourly intervals does not materially influence the acuity of hearing. A 45 gr. dose, taken in 15 gr. doses one half-hour apart, produces in five hours pronounced tinnitus—defined as a subjective sound like locusts singing in the trees — a more marked sensation of fullness in the ears, and a pronounced decrease in acuity, particularly for high-pitched sounds (1000-1800). A total dose of 75 gr. taken in sub-divided doses within a few hours, also produces a pronounced decrease of acuity, appearing to affect the lower part of the scale (256-1000) more markedly than the upper (1000-1800). It would, however, be difficult to be sure of the amount of the drug absorbed. It was found

that the amount of actual loss of acuity of hearing was not proportionate to the loudness of the tinnitus. After hearing returned to normal, the tinnitus continued for at least 24 hours. It is well known that tinnitus may be produced by exposure to loud sounds. A person was placed for three and a half hours with his head three feet in front of a telephone receiver which emitted an extremely loud note (1300), so loud that it could be heard outside the building. The tinnitus and sensation of fullness in the ears was as apparent as in the 40 gr. quinine test, and did not entirely disappear for 36 hours. The tinnitus so produced does not bear any definite pitch relation to the frequency of the sound causing the condition. The acuity of hearing was not impaired after the three and a half hours' exposure. Recovery of normal hearing after ingestion of quinine occurs in 24 to 36 hours. The toxic actions of quinine affect not only the auditory sense, but the entire nervous apparatus, so that definite readings with larger doses are not possible.

(Lancet, London, March 27th, 1923, Vol I, No. 12, pp. 605—606.
Annotations)

TREATMENT OF PHAGEDENA
WITH INTRAVENOUS INJECTIONS OF QUININE

(ZUR BEHANDLUNG DES PHAGEDÄNISMUS
MIT INTRAVENÖSEN CHINININJEKTIONEN)

BY

Prof. A. BUSCHKE, M.D., Berlin

IN an earlier report (*Deutsche Medizinische Wochenschrift*, 1921, No. 15) I have drawn attention to the growth of phagedena in my experience. Though perhaps the increase in these conditions has not since been very marked, I have certainly come across cases more frequently than previously. Apart from genital and perigenital affections, I include also noma and Plaut-Vincent's angina. To this category hospital gangrene perhaps also belonged. The aetiology has up till now not been accurately determined. The fuso-spirillar symbiosis associated with these conditions, appears to me to be merely accidental, at any rate, not the primary cause, aggravating the process perhaps. On a few occasions we located the Matzenauer bacilli, but as these are not to be found very often, it is questionable whether they are the primary cause either. It is doubtful whether phagedenic chancres in syphilis are to be considered as a combination, or whether the luetic contagion can—of itself—under suitable conditions, produce the phagedenic change of the primary affection. Similarly as regards *ulcus molle*. In any case in the great majority of cases the phagedenic ulcer is not to be identified with *ulcus molle*, either aetiologically or as regards infectiousness. Many clinical observations sug-

gest that there may be an unknown, perhaps invisible contagion, possibly—in relation to the tropical endemic form—of a protozoal nature. The constitution of the patient cannot be a decisive factor, as frequently very strong and otherwise healthy people fall ill and even die from this infection. It is remarkable that—according to my experience—there has, so far, been no case which has proved that phagedena can be conveyed from man to man.

I distinguish two forms:

1. A mainly local affection without general symptoms or with very slight ones. This is — for the most part — comparatively benign, yielding to more or less prolonged treatment with vinum camphoratum, iodoform, ustions, cauterisations with chloride of zinc. Local treatment with eucupin was ineffective, perhaps rivanol is better. Even here however, I have encountered one case which was refractory, and had a fatal issue.
2. Cases with severe general symptoms accompanied by high fever, marked prostration and a general septic condition. In these, in addition to the local therapy above-mentioned, we tried the most diverse treatments—salvarsan, collargol, protein substance, quinine internally — with little effect worth mentioning and we had several fatal results.

Of late, we have treated those severe cases whose prognosis according to my earlier experiences was not good, with *intravenous injections of quinine*, and have observed such a quick and favourable response that I recommend this treatment in addition to the local therapy. It is possible that the local condition is considerably improved by it but this is not certain. On the other hand, the general condition has

frequently been favourably influenced. Be that as it may, we have since had no more fatal cases to report. The quinine is dissolved in urethane and intravenous injections of 0,3—0,5 up to 1.0 gram administered per diem, continuing this treatment for a time after disappearance of the fever. Just this last point seems to be of great importance, as in one case now under observation, the patient suffered a relapse when we discontinued too soon. Further quinine treatment soon put this right.

I wish particularly to mention that one case in which several weeks after complete recovery, the patient feeling quite well there was without any local recurrence a general relapse, which soon afterwards disappeared. Bacteriological examination of the blood was in all cases negative, but the last observation proves that there must be circulating in the body a contagion which would account for the general disturbance.

(Klinische Wochenschrift, Berlin, August 27th, 1923, p. 1675)

THE EXPERIMENTAL BASIS OF PERSONAL
SYPHILIS PROPHYLAXIS(DIE EXPERIMENTELLEN GRUNDLAGEN
DER PERSÖNLICHEN LUESPROPHYLAXE)

BY

WERNER WORMS, M. D., Berlin

Berliner Medizinische Gesellschaft, own report of the
meeting, held March 7, 1923

AFTER a general outline of the routine protective measures in the development of which special credit is due to *Schereschewski* the speaker remarked that lately quite a number of prophylactic preparations had been put upon the market and it was of great importance that these should be investigated with a view to determining their value and suitability for the purpose. There are three methods of examination each of which the lecturer discussed in detail.

The first method is to discover the effect of the treatment on spirochaetes taken from the affected serum in dark ground illumination. The procedure is to establish contact between the drop the affected serum and the drop of the remedy and to watch the result at the point of contact. This method is only of value so long as the surrounding spirochaetes display good mobility. Under this test *Metschnikoff's* calomel-lanolin cream failed, showing no effect, *Schereschewski's* quinine ointment (40%; Deutsche Medizinische Wochenschrift, 1913, No. 27, p. 1310) immediately killed the spirochaetes while Spirogon ointment — containing vuzin — displayed a powerful but varying action.

The second method is to ascertain the influence of the prophylactic on the spirochaetes of a syphiloma in man or animal. Here too the calomel cream displayed no action, whereas *Schereschewski's* quinine ointment was found highly effective. The other preparations proved to be either ineffective or inconstant.

The third method consists of experiments on animals. Formerly these had been carried out on monkeys, but as monkeys now cost prohibitive prices, rabbits are used — though these too, by the way, cost 10.000 Marks a piece. The work on rabbits is done either with “original spirochaetose”, a disease closely resembling human syphilis, or with human spirochaetes with which the rabbits have been inoculated. On this method just as well the quinine ointment gave admirable results.

With a view to economising the animals as far as possible, recurrent infection of white mice is often resorted to as a test of the proposed prophylactic. This method however must be condemned in view of the other unobjectionable test methods referred to above having regard to the difference between the true syphilitic spirochaete and the spirochaete recurrentis.

As the new German law renders an official examination of prophylactics obligatory, this misleading test adopted by the government clinics should be discarded because of the far-reaching consequences of the certificates issued.

In the discussion which followed *Schereschewski* emphasised strongly the inadmissibility of state certificates based on the recurrent method.

Lesser maintained that potassium permanganate and acetate of alumina also effectually destroy the spirochaetes and

criticised the protective routine in present use, directing particular attention to the favourable statistics obtained in the English and American Armies with calomel ointment which if we are to accept the results reported by *Schere-schewski*, was absolutely useless.

Leonhard recommended the recurrent test as being especially valuable in determining the value of prophylactic measures against syphilis. Still better is the "spirochaete cuniculi", which cannot, however, be transmitted naturally, as the female rabbit will only allow the male to approach her during the mating season with the result that the possibility of an examination being undertaken is very much reduced. Communication of the infection may be, however, accomplished by artificially effecting contact of the sexual parts.

(Münchener Medizinische Wochenschrift, March 16th 1923, No. 11, p. 346)

ON THE EFFECT OF QUININE ON THE DENTAL PULP

(ÜBER DIE WIRKUNG DES CHININS AUF DIE ZAHNPULPA)

A DETAILED ENQUIRY BY

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FOR anaesthetising or killing the tooth pulp to admit of its removal, three methods are in use :

1. Killing the pulp with arsenious acid.
2. Pressure anaesthesia with cocaine adrenalin solution.
3. Anaesthetisation by injection of novocaine adrenalin solution or similar preparations (Eusemin, Lindesin etc.)

Which of these three methods is used in any particular case depends on the more limited diagnostics.

The arsenious acid, usually made into a paste with cocain is applied on the naked pulp, and sealed in the prepared cavity. This method has the advantage that co-operation of the patient is but little required — and this is a consideration with nervous patients. No pain is experienced throughout the 2—3 days which the arsenic requires to take effect. Most authors prefer the arsenic paste to-day, presumably because it seems to them desirable that the pulp should be cauterised with arsenious acid directly, and because they believe that this cauterisation creates a distinct line of demarcation against the periosteum. Further, many supporters of the pulp amputation method make the result of the amputation dependent on this previous arsenious acid treatment, an opinion which is distinctly stressed by *Weiser* but with which, however, I am not in agreement.

The method of pressure anaesthesia — in which a small pad damped with a concentrated solution of cocain adrenalin, is pressed on the pulp and then sealed with unvulcanised — rubber is excellent. The initial pain — generally caused by the effect of the pressure — usually only lasts a few seconds. The method is not always possible, e.g. in unfavourably situated flat cavities. It is also ineffective where severe pulpitis or denticulate formations exist.

As regards the third method, it is superfluous to say that with a good anaesthesia by injection the pulp can be extirpated straight away. There are only few cases in which the injection anaesthesia cannot be made: e.g. in nervous, hysterical patients, also in those who display idiosyncrasy to alkaloids; those particularly who have been unable to sleep for several nights by reason of pain, often react to the injection with faintness or conditions of excitation. In diseases of the heart and the vascular system (arteriosclerosis) it is, of course, well known that considerable care has to be exercised with injections.

The dentist chooses one of the three methods according to his experience.

We have undertaken the investigation of the action of various substances on the dental pulp with a view to replacing the first, the arsenious acid method, by another i.e. we wanted to find a method which can be relied on to anaesthetise or kill the pulp to a certainty with equal painlessness.

The use of arsenic — in certain circumstances — may cause grave complications. We know for instance the necrosis of the dentinal papillae and the alveolar septum if merely a little of the arsenic paste gets accidentally into the inter-dental spaces; we know, too, the periostal dis-

turbances if the paste is allowed to remain in contact too long. I want also to direct attention to the fact that a number of fatalities have occurred which are easily traceable to a portion of the arsenic paste having been swallowed.

After having myself tried for several years anaesthetisation by pressure and injections, I fell back more frequently on the destruction of the pulp by arsenious acid. It is to-day still the least painful and most certain method for the patient.

The first remedy we used to replace arsenious acid was quinine. We prepared a paste made from quinine hydrochlor., tragacanth. and creosote¹, on which I report as follows.

I repeat that the task I made was to modify the simplest and least painful method of pulp extirpation, i.e. the use of arsenious acid, by replacing the dangerous arsenious acid by another agent just as easy of application, while yet retaining all the advantages of this method. Quinine was chosen as in pharmacology a certain analogy is demonstrable between the effects of quinine and arsenic.

Before I detail the pharmacological effects of quinine I would like to mention a few other remedies which were used as well as arsenious acid, for the same considerations as mentioned before, and which — so to speak — precede before my experiments. We will not mention now the remedies, used in the infancy of dentistry.

I must mention two remedies — nervocidine and certain quinine derivatives.

¹ Actually I use quinine paste as follows: make the quin. hydrochlor. into a semi-solid paste with a neutral oil — usually oleum lini, or again oleum sesami, or very often oleum sesami and oleum caryophyllae.

Nervocidine was introduced into therapy by *Dalma* as a remedy equal to arsenic. It is manufactured from a plant grown in the interior of India. A solution of nervocidine gives an alkaloidal precipitation, hence the active principle is an alkaloid. The remedy has been used in some institutes, as also in the Dental University Institute of Vienna. According to *Kaas*, it might be applied to the pulp cavity for several months, though as a rule after a comparatively short time the pulp could be removed. There were however often failures. All authors agreed that the "painful stage of the arsenic action" is absent with nervocidine. Undoubtedly *Kaas* frequently observed this "painful stage" with nervocidine. In the front teeth the extraction of the canal pulp was almost painless. The tooth was but little discoloured afterwards. In contrast with these advantages the effect was however, just as uncertain as with arsenic.

Scheff—see literature—used nervocidine with eugenol. He agreed that the treatment has many advantages, e.g. there were no after pains, while on a long application no periosteal irritation resulted. Further, the remedy took effect without being applied directly to the pulp. On the other hand, he found considerable disadvantages, as that it had to be applied *repeatedly* in the pulp cavity. After the pulp removal there was always a violent post-haemorrhage, and finally he observed gingival necrosis, and small pustules on the tongue. The absolutely allaying effect on the pulp is—according to *Scheff*—due to the "anaemiating" action of nervocidine. He observed that ulcerations of the cheeks after application of nervocidine, were never so severe as the necroses on the mucous membrane caused by arsenious acid.

Madzsar and *Balassa* stated that if portions of the nervocidine get into the stomach, vomiting results.

It is interesting to record that microscopically, no changes could be found in the pulp.

Some authors supported nervocidine, however, as they thought to find a preparation which might replace arsenic paste. This hope has not been fulfilled and the use of nervocidine ceased after a comparatively short time, almost entirely. Indeed after 1903, it does not appear in any literature.

Quite recently the *Morgenroth* quinine derivatives (eucupin and eucupinotoxine) have been experimented with for the above purpose. *Brühn* applied concentrated solutions on the pulp without attaining a special result. I reproduce verbatim an extract from his very detailed and comprehensive work in which he sums up the results of his extensive researches.

“Originally we also hoped that it would be possible in pulpitis to eliminate the sensibility of the living pulp by the application of eucupin instead of arsenic so that extraction could be undertaken. The eucupin was applied as a pulp anaesthetic.

“As an experiment we excavated affected teeth at first only so far that the pulp was just touched, and subsequently (by means of cocaine dentin anaesthetisation) removed a large part from the roof of the pulp-cavity and laid directly on the pulp a swab saturated with a 5% eucupin solution, which had been rolled finally in pure eucupin; we used eucupinotoxine in the same way leaving it “in situ” up to 2 days. The result was everywhere negative. The use of eucupin for 10 minutes caused no appreciable diminution of sensibility. After 1—2 days application the pulp appeared superficially crusted over and a portion

of the crown pulp seemed insensible against all attacks. But as soon as we penetrated deeper with the nerve needle, the pulp reacted unmistakeably so that extirpation was not be thought of. The reports of the patients on their subjective feelings under the influence of the eucupin, was that the pains caused by the inflamed pulp ceased after $\frac{1}{2}$ to 4 hours; later on, however, after 5 to 10 hours the pains were worse. This apparently, was attributable to the commencing local irritation of the tissues due to the strong application. In objective agreement with this was a marked hyperaemia of the deeper-seated and uncauterised portions of the pulp, indicating an existing or progressive inflammation of the root pulp. Therefore even the strongest solutions of eucupin and eucupinotoxine are not in their anaesthetic effect adequate to render pulp extirpation possible."

Quinine was chosen as the first preparation, as it has a tissue-necrotic action similar to arsenious acid.

The following is extracted from *Meyer-Gottlieb's Experimental Pharmacology*:

"The chief result of these investigations may perhaps be summed by saying that quinine impedes and retards the whole of the vital processes anabolic as well as catabolic; therefore in minute doses it exercises a conservative influence on the entire vital process, while in larger doses it is generally a protoplasmic poison, completely destructive of metabolism. On what elementary principle this rests is absolutely unknown. We only know that this can be observed with nearly all organisms of higher and lower plants and from the protozoa upwards."

Cases, coming into the Clinic nearly all with severe acute pulpitis, were experimented with. In these cases, after

laying the cavity open, the carious layers were excavated, as far as possible, and a piece of quinine paste about as big as a pinhead was laid directly on the pulp — which was sealed with Fletcher or cotton wool. The paste was used in 30 cases of acute pulpitis between the middle of December 1921 and the beginning of April 1922.

In order to test the durability of the paste, I commenced in November again a series of experiments, and tried its effect in a further seven cases.

Before I conclude with my final results, I should like to submit a few cases from which it is very easy to deduce the nature of the effect obtained.

Case 1. R. R., physician. Left upper wisdom tooth $\overline{18}$, profound caries. No spontaneous pains.

21. XII. 1921. When excavating there was severe pain, and bleeding pulp. Quinine paste.

22. XII. Quinine paste.

23. XII. Severe pulp haemorrhage, marked sensibility to pain. On the previous day there was barely perceptible pain for about half an hour. Again quinine paste.

24. XII. No more bleeding when opening the pulp cavity, complete insensibility. Palatine pulp entirely anaesthetised. No bleeding after removal of the palatal pulp nerve.

Case 4. D. J. Severe pains for several days. Peripheral cavity in $\underline{6}$, pulp open.

28. XII. Quinine paste.

29. XII. Insensibility. After drilling the pulp the palatine pulp nerve was removed with severe pain. The nerve appeared to be somewhat bloodless. Slight haemorrhage after removal.

Case 7. P. L. Pulpitis in the right upper II. inc. Had suffered pain for some time, lately very severe.

3. I. Quinine paste. Pulp bleeding exposed.

4. I. Pulp cavity opened painlessly. Rootpulp removed, with resulting bleeding.

Case 9. L. J. Left upper II. premolar.

2. I. Severe pain.

3. I. Quinine paste.

4. I. Pulp exposed, nerve extracted painlessly. Severe bleeding.

Case 13. F. G. Left upper I. premolar. Pain for two weeks, patient did not sleep the previous night.

5. I. Quinine paste. Absolutely without pain.

7. I. Pulp very sensitive. Treatment impossible. Quinine paste.

10. I. On examination, pulp still somewhat painful, no bleeding. Quinine paste again.

12. I. Drilling the pulp cavity. Severe bleeding and pain. Quinine paste once more.

13. I. Pain on exploring the root canals. Fletcher's *Arsenic*.

Case 15. K. R. Right upper I. molar. Pain for two weeks. Patient could not sleep for several nights.

9. I. Quinine paste.

11. I. No pain at home. On exploring, pulp painful. No bleeding. Quinine paste once more.

16. I. In the meantime no pain, but on examining pulp still painful. *Arsenic*.

Case 19. L. V. Left upper I. premolar. Severe pain for a week, patient could not sleep at night.

9. III. Cavity is laid open. Quinine paste.

10. III. After applying paste, *slight* pain, especially on changes of temperature. Once more quinine paste.

14. III. Meantime no pain. On drilling pulp, pain. Quinine paste.

21. III. No pain. Drilling the pulp cavity was possible but painful when drilled deeper. *Arsenic*.

Case 20. Ph. S. Left lower I. molar. Pain for a week. Patient has not slept for two nights.

14. III. Quinine paste.

17. III. No pain at home. Exploring painful. Quinine paste.

20. III. Same condition. *Arsenic*.

Case 29. B. Right lower II. molar. Pain for 3 days. Patient could not sleep in the night.

21. III. Quinine paste.

28. III. No pain at home. Opening of pulp cavity possible. Tricresol Formalin pad. (Pulp-amputation).

Case 3a. E. S. 27. XI. 1922. For one week pain in $\bar{L}$. Patient did not sleep in the night. Quinine paste.

30. XI. Absolutely no pain since applying paste. Examination of pulp still painful. Renewed application of quinine paste.

5. XII. Patient quite free from pain.

13. XII. Still free from pain. Exploration of pulp painful. Pulp bleeding.

19. XII. Extirpation of pulp with anaesthesia by injection.

Case 5a. P. B. Left lower I. molar. Pain for 3 weeks.

28. XI. Quinine paste. Fletcher.

1. XII. Patient free from pain.

11. XII. Patient free from pain, in the meantime. Exploration is painful. Markedly diminished sensibility. Pulp slightly bleeding; again quinine paste.

18. XII. Slight pains after hot water. Exploration is painful. Drilling of pulp cavity partly possible. Diminished sensibility; severe pulp bleeding. *Arsenic*.

Case 6a. B. K. Right upper II. molar. Excavated, pulp exposed.

28. XI. Quinine paste.

1. XII. Patient continues without pain.

17. XII. Patient complains of pain on eating or when drinking cold water. Extraction of the palatine rootpulp with injection anaesthesia: no bleeding. Rootpulp is an odourless brownish coloured thread, slightly tinged with blood in the middle.

From these cases we can form our opinion of the effect of quinine.

Quinine cannot replace arsenious acid to mortify the pulp. Even after remaining under its influence for several weeks, the pulp is still, in most cases, sensitive, bleeding and living. In a small percentage it was only possible to open the crown pulp cavities, however, with more or less

severe pain. Only in a few cases could direct extirpation of rootpulp be undertaken, and always with varying degrees of pain. In the majority of cases, arsenious acid had eventually to be applied or the pulp removed under injection anaesthesia.

On the other hand quinine has a pronounced analgesic effect on the inflamed pulp. Nearly all my cases were of severe pulpitis, and quinine paste did not fail in a single instance. The patient was free from pain for weeks after application, though in a few cases — this too after weeks — there was a slight sensibility to cold or warmth.

Besides, the pulp remains living. Indeed several weeks after, the pulp, except for necrosis at the point of application, was bleeding and sensitive. The fact that in a few cases mummification of the pulp was found to have taken place, should not disarrange us, as there is the presumption that in a few of the many severe pulpitic conditions, the paste was only applied when partial or complete gangrene had taken place.

So far as the quantities are concerned, *the quinine paste naturally is an absolutely non irritating and harmless remedy*, so that an accidental dislodgement of smaller or even larger particles on to the mucous membrane or swallowing them can do no harm.

While it is true that quinine bears a certain resemblance in its result to nervocidine, it is nevertheless far superior to this treatment by reason of its absolutely certain analgesic effect and complete harmlessness.

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(Zeitschrift für Stomatologie, Berlin & Vienna, XXI, No. 3. March 1923, pp. 159—166)

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PRINTED IN THE PRINTING OFFICE OF J. H. DE BUSSY
THE HELIOTYPES ARE MADE BY L. VAN LEER & Co.
THE BINDING AND TITLE-PAGE WERE DRAWN BY H. VAN DEN BOSCH
THE BINDING WAS DONE BY ELIAS P. VAN BOMMEL
AMSTERDAM

